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Palladium-Catalyzed C-C Bond and C-S Bond Forming Reactions of Sulfoxides

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Abstract
Transition metal catalyzed C-C bond and C-S bond forming reactions offer a new opportunity to construct sulfur-containing compounds. However, preparation of sulfoxides through this pathway remains sporadic, probably due to the very weakly acidic -protons or instability of sulfenate anion, a key nucleophile to produce sulfoxides. To this end, this dissertation investigated the novel approaches to prepare sulfoxides via palladium catalyzed -arylation of methyl sulfoxides and S-arylation of sulfenate anions.

In chapter 1, the palladium catalyzed alpha arylation of unactivated sulfoxides is introduced. The weakly acidic alpha protons of sulfoxides are reversibly deprotonated by LiOtBu, and an indole-based phosphine ligated palladium complex facilitates the arylation reactions. A variety of (hetero)aryl methyl sulfoxides were successfully cross coupled with aryl bromides. More challenging coupling partners, such as alkyl methyl sulfoxides (including DMSO) proved to be suitable under the optimized conditions. Moreover, aryl chlorides were employed as electrophiles in our protocol by using Buchwald-type precatalyst. This method was utilized to synthesize bioactive benzyl sulfoxide intermediates

In chapter 2, we presented a novel approach to produce diaryl sulfoxides from aryl benzyl sulfoxides. Optimization of the reaction conditions was led by High-Throughput Experimentation (HTE) techniques. A single Pd(dba)2/NiXantPhos based catalyst successfully promotes a triple relay process involving sulfoxide -arylation, C-S bond-cleavage, and C-S bond-formation. Byproduct benzophenone is formed by an additional palladium-catalyzed process. It is noteworthy that palladium catalyzed benzylative substitution to cleavage C-S bond of sulfoxides is unprecedented. A wide range of (hetero)aryl benzyl sulfoxides, as well as alkyl benzyl sulfoxides with various (hetero)aryl bromides were employed in the triple relay process in good to excellent yields (85-99%). Moreover, aryl methyl sulfoxides, dibenzyl sulfoxides and DMSO could be utilized to generate diaryl sulfoxides involving multiple catalytic cycles by a single catalyst.

In chapter 3, we investigated diaryl sulfoxides generation from aryl benzyl sulfoxides and aryl chlorides via three sequential catalytic cycles all promoted by a NiXantPhos-based palladium catalyst. The key step is S-arylation of a sulfenate anion. An air- and moisture-stable palladacyclic precursor derived from NiXantPhos efficiently facilitated the transformation. Various functional groups, especially those with acidic protons, were tolerated. This method can also be extended to methyl and dibenzyl sulfoxides substrates

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PALLADIUM-CATALYZED C–C BOND AND C-S BOND FORMING REACTIONS OF SULFOXIDES

Tiezheng Jia

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Supervisor of Dissertation

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Graduate Group Chairperson

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Professor Gary A. Molander, Hirschmann-Makineni Professor of Chemistry

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Professor Madeleine M. Joullie, Professor of Chemistry
Professor Gary A. Molander, Hirschmann-Makineni Professor of Chemistry
Professor William P. Dailey, Associate Professor of Chemistry

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Dedicated to my family

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ABSTRACT

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Transition metal catalyzed C-C bond and C-S bond forming reactions offer a new opportunity to construct sulfur-containing compounds. However, preparation of sulfoxides through this pathway remains sporadic, probably due to the very weakly acidic α-protons or instability of sulfenate anion, a key nucleophile to produce sulfoxides. To this end, this dissertation investigated the novel approaches to prepare sulfoxides via palladium catalyzed α-arylation of methyl sulfoxides and *S*-arylation of sulfenate anions.

In chapter 1, the palladium catalyzed α-arylation of unactivated sulfoxides is introduced. The weakly acidic alpha protons of sulfoxides are reversibly deprotonated by LiO^tBu, and an indole-based phosphine ligated palladium complex facilitates the arylation reactions. A variety of (hetero)aryl methyl sulfoxides were successfully cross coupled with aryl bromides. More challenging coupling partners, such as alkyl methyl sulfoxides (including DMSO) proved to be suitable under the optimized conditions. Moreover, aryl chlorides were employed as electrophiles in our protocol

by using Buchwald-type precatalyst. This method was utilized to synthesize bioactive benzyl sulfoxide intermediates

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Chapter 1 Palladium-Catalyzed Direct α-Arylation of Methyl Sulfoxides with Aryl Halides

1.1 Introduction

1.1.1 Introduction to Sulfoxides

Sulfoxides exhibit a wide range of biological properties, including anticancer,[1a-d] anti-virus[1e] and anti-bacteria activity,[1f] and are useful bioisosteres (Figure 1-1).[2] They also serve as versatile intermediates in organic chemistry and have been widely used as ligands in catalysis.[3]

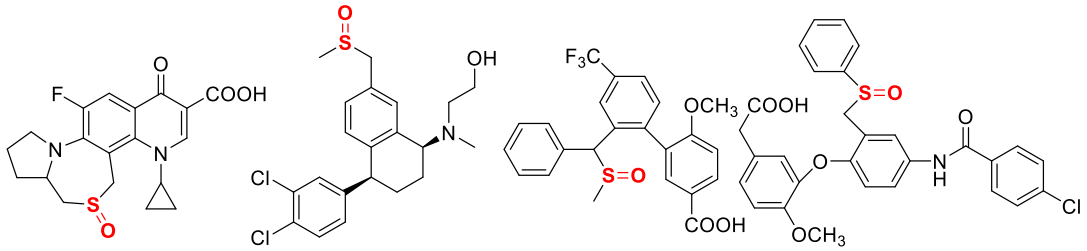
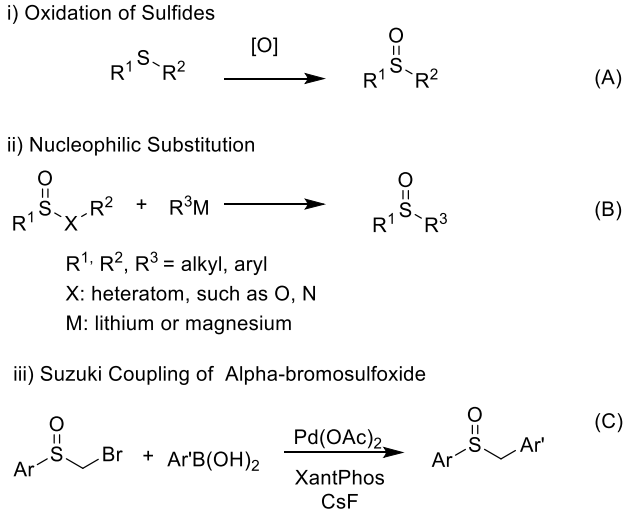


Figure 1-1. Representative Sulfoxides Exhibiting Bioactivities.

The two most common approaches to generate sulfoxides are i) oxidation of sulfides[4] and ii) substitution reactions of electrophilic sulfoxide derivatives with organometallic nucleophiles[5] (Scheme 1-1A&B). Despite the popularity of these methods, both suffer from the limited functional group tolerance, because either strong oxidizing agents or reactive organolithium or Grignard reagents are employed. Benzyl phenyl sulfoxides were also accessed by a Pd-catalyzed Suzuki cross-coupling

employing prefunctionalized coupling partners (Scheme 1-1C).[6] A more efficient and atom-economical route to benzyl sulfoxides would be the direct arylation of methyl sulfoxides.

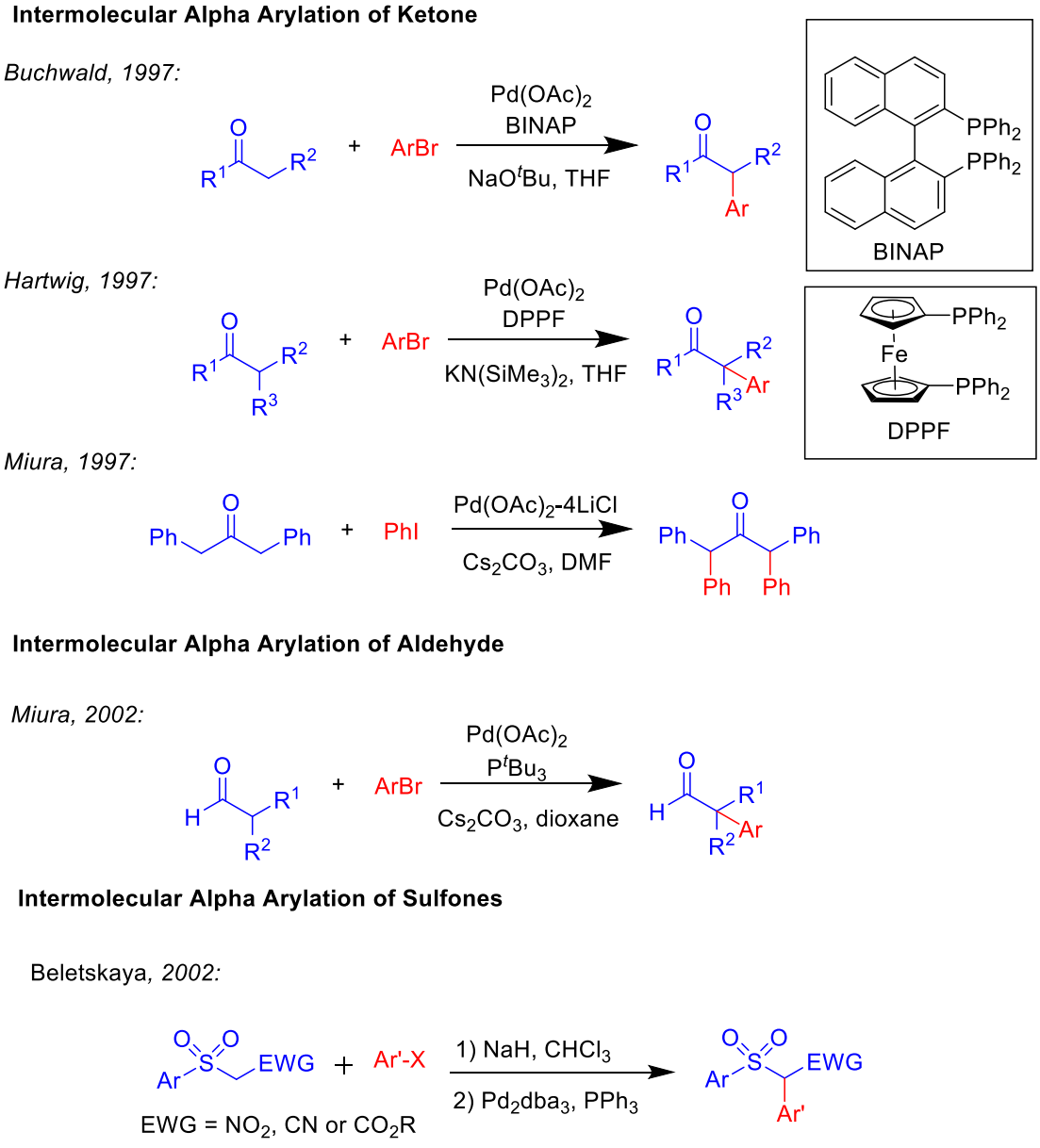


Scheme 1-1. Previous synthetic approaches to sulfoxides.

1.1.2 α-Arylation of Carbonyl Compounds and Sulfones

In 1997, the unprecedented intermolecular α-arylation of ketones was reported by Buchwald, Hartwig and Miura groups simultaneously (Scheme 1-2). Slightly different catalysts were employed in this transformation, but the α-protons were deprotonated by base (NaO^tBu, $KN(SiMe_3)_2$, or Cs_2CO_3), and then the catalysts facilitated the following steps. Since the seminal works by Buchwald, Hartwig and Miura, α-arylation of carbonyl compounds has emerged as a reliable approach to construct molecules that are difficult to make in traditional methods. Various functional groups have been successfully explored to be incorporated into the reservoir of α-arylation

reactions. In 2002, Beletskaya and coworkers reported the first example of α-arylation of activated sulfones (Scheme 1-2) using a Pd/PPh_3-derived catalyst. Since the α-protons were activated by both sulfone and another electron-withdrawing group, the pK_a is in the range of 7.1–12.2. To our surprise, despite the similarity of this approach to the well-known α-arylation of carbonyl compounds and sulfones, the α-arylation of sulfoxides is unknown.

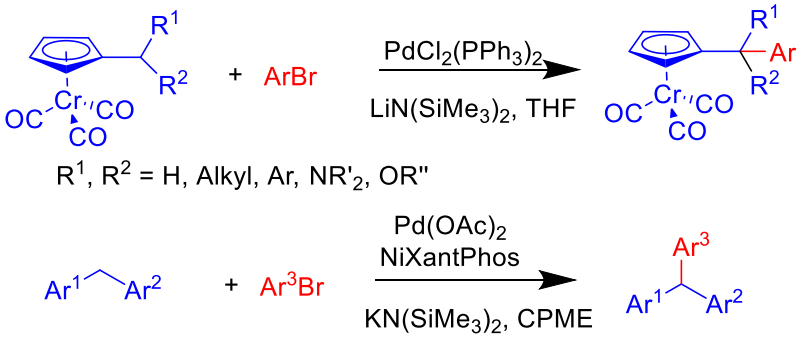


Scheme 1-2. Palladium catalyzed α-arylation of ketones, aldehydes, and sulfones.

1.1.3 Our Approach to α-Arylation of Sulfoxide

In the case of methyl phenyl sulfoxide (pK_a 33 in DMSO[10c]), even stronger bases are used for deprotonation, such as LDA,[11a,b] LiN(*i*-Pr)(*c*-Hex),[11b] or *n*-BuLi.[11c] These bases, however, are less practical for cross-coupling reactions because of their limited compatibility with catalysts and coupling partners. The challenge to develop the direct alpha arylation of unactivated sulfoxides is to identify a suitable combination of base and catalyst.

We recently introduced approaches to the direct arylation and allylation of weakly acidic benzylic hydrogens of η^6-arene complexes of toluene, benzylic amines, benzylic ethers and diphenylmethane derivatives (Scheme 1-3).[12] Diphenylmethane derivatives were arylated via a deprotonative cross-coupling procedure (DCCP), even in the absence of arene activating metals.[13] The DCCP entailed a reversible room temperature deprotonation of the weakly acidic benzylic protons of diphenylmethane (pK_a 32) with concurrent palladium-catalyzed cross-coupling. Based on the success of this method, we envisioned a palladium-catalyzed direct α-arylation of methyl sulfoxides with aryl halides via DCCP.



Scheme 1-3. Palladium Catalyzed η^6-arene complexes of toluene, benzylic amines, benzylic ethers and diphenylmethane derivatives via DCCP

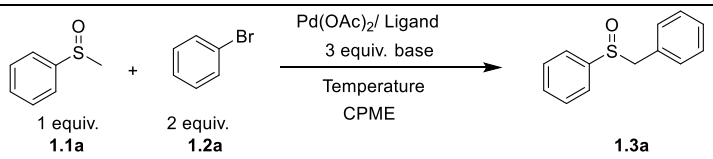
1.2 Results and Discussion

1.2.1 Optimization of Palladium Catalyzed α-Arylation of Methyl Sulfoxides

Based on the success of DCCP of diarylmethanes, we initiated efforts for the cross-coupling of sulfoxide **1.1a** with 4-*tert*-butyl bromobenzene (**1.2a**) employing similar reaction conditions to the DCCP with diarylmethanes in the absence of arene activating metals[13] [$KN(SiMe_3)_2$, cyclopenyl methyl ether (CPME), 10 mol % $Pd(OAc)_2$, 15 mol % NiXantPhos, Table 1-1, **1.L1**]. The coupled benzyl sulfoxide product (**1.3a**) was formed in 27% isolated yield at 80 ^oC (Table 1-1, entry 1). To build on this promising result, we screened 6 bases (LiO^tBu, NaO^tBu, KO^tBu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$) and 4 solvents using microscale High-Throughput Experimentation (HTE) techniques. The leading base from this screening was LiO^tBu in CPME, generating the desired product (**1.3a**) in moderate yield (42%, Table 1-1, entry 2). The search for more active catalysts was continued

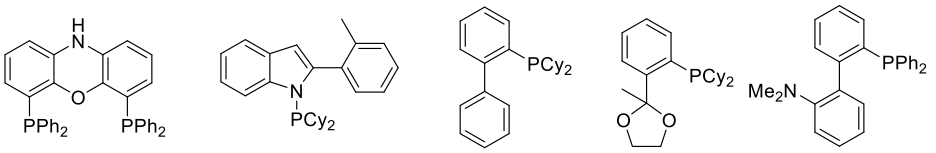
with LiO^{t}Bu and CPME by testing a series of sterically and electronically diverse mono- and bi-dentate ligands. Of the 112 ligands examined, **1.L2**–**1.L5**[14] were promising (see Experiment Section for details), with *N*-(dicyclohexylphosphino)-2-2'-tolylindole (**1.L2**) outperforming the others (Table 1-1, entry 3 *vs.* 4–6). To the best of our knowledge, this monodentate, bulky, and electron-rich phosphine ligand, introduced by Kwong and coworkers, has only been successfully employed in one study of the Suzuki-Miyaura cross-coupling reaction.[14b] The microscale result using **1.L2** was successfully translated to laboratory scale, rendering product **1.3a** in 75% isolated yield. A decrease in temperature (entry 7) or catalyst/ligand loading (entry 8) was detrimental to the yield under these conditions. We next focused on the identification of more suitable palladium sources, substrate ratios, and temperatures. Of the conditions and ratios examined, better results for the direct alpha arylation were obtained on microscale employing $Pd(OAc)_2$ (10 mol %), ligand **1.L2** (15 mol %) and a **1.1a**:**1.2a** of 1:2 at 110 ^oC. Scaling the reaction to 0.1 mmol and increasing concentration from 0.1 M to 0.2 M resulted in isolation of the benzyl sulfoxide with 93% yield (entry 9). A further increase in the concentration to 0.3 M resulted in slightly lower yield (87%, entry 10), probably due to reduced solubility of the sulfoxide and base at this concentration. Therefore, 0.2 M was chosen for the substrate scope study.

Table 1-1. Optimization of α-arylation of methyl phenyl sulfoxide (**1.1a**).



Entry	Ligand	Base	Catalyst/ligand /mol %	Concentration /M	Temp. /°C	Yield[a] /%
1	**1.L1**	$KN(SiMe_3)_2$	10/15	0.1	80	27
2	**1.L1**	LiO^{t}Bu	10/15	0.1	80	42
3	**1.L2**	LiO^{t}Bu	10/20	0.1	110	75
4	**1.L3**	LiO^{t}Bu	10/20	0.1	110	16
5	**1.L4**	LiO^{t}Bu	10/20	0.1	110	23
6	**1.L5**	LiO^{t}Bu	10/20	0.1	110	44
7	**1.L2**	LiO^{t}Bu	10/20	0.1	80	40
8	**1.L2**	LiO^{t}Bu	5/10	0.1	110	40
9	**1.L2**	LiO^{t}Bu	10/20	0.2	110	93[b]
10	**1.L2**	LiO^{t}Bu	10/20	0.3	110	87

[a] Yield determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield after chromatographic purification.

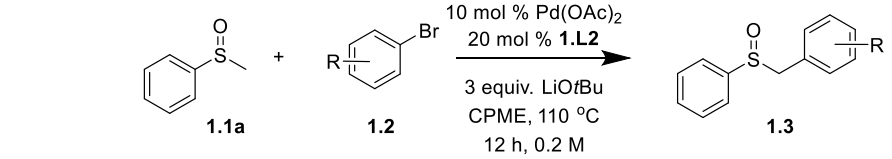


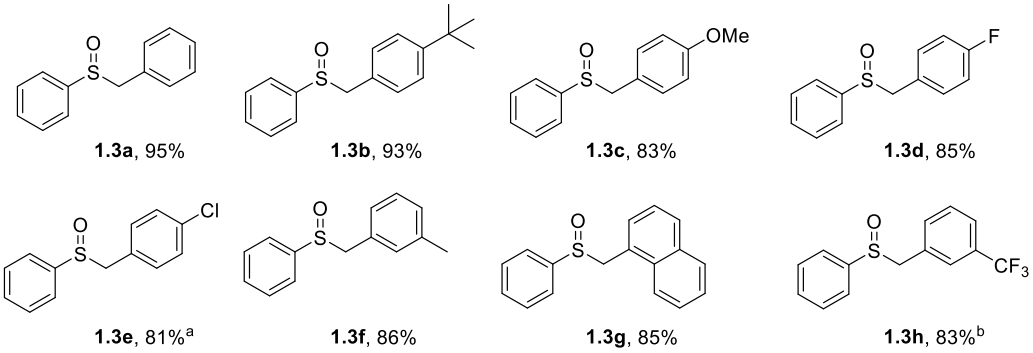
NiXantPhos (**1.L1**) Kwong's ligand **(1.L2)** Cy JohnPhos (**1.L3**) **1.L4** Ph DavePhos (**1.L5**)

1.2.2 Substrate Scope of Aryl Bromides in Palladium Catalyzed α-Arylation of Methyl Phenyl Sulfoxide (1.1a)

Under the optimized conditions in entry 9 (Table 1-1), the scope of the direct arylation of methyl phenyl sulfoxide (**1.1a**) with various aryl bromides was investigated (Scheme 1-4). A wide range of substrates exhibited excellent reactivity, including those with electron-donating (**1.3b**, **1.3c**), electron-withdrawing (**1.3d**, **1.3e**, **1.3h**), and *ortho*- or *meta*- substitutents (**1.3g**, **1.3f**). In the case of 4-chloro bromobenzene, 0.1 M concentration was found to be optimal for chemoselective activation of the bromide, providing **1.3e** in 81% isolated yield.

Scheme 1-4. Substrate scope of aryl bromides in Pd-catalyzed α-arylation of unactivated sulfoxides.



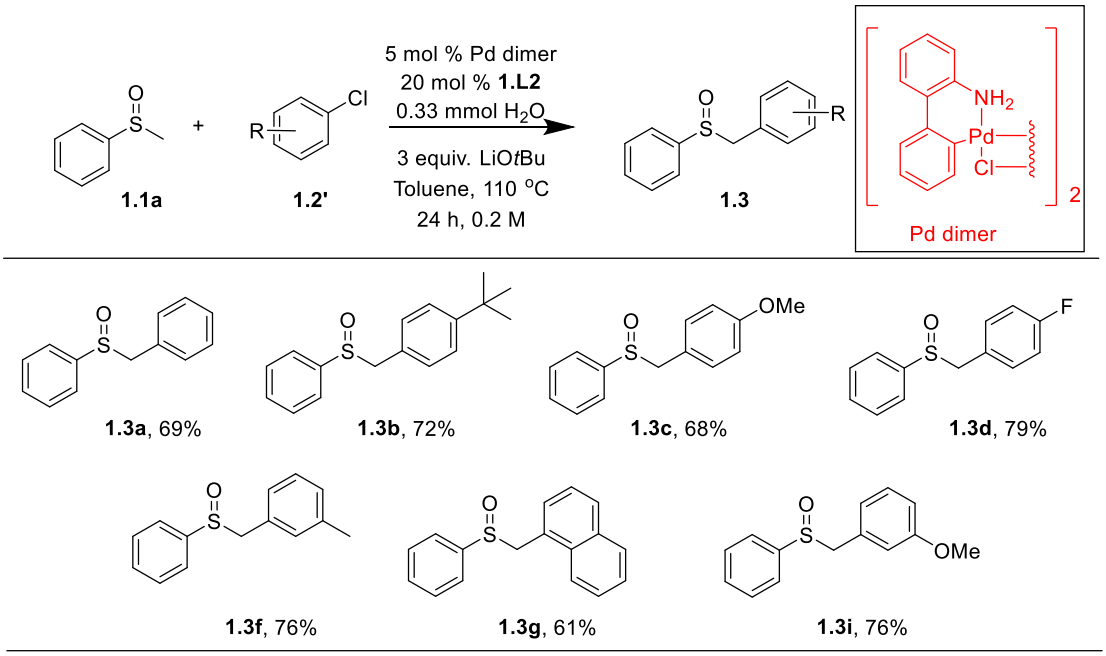


[a] 0.1 M, 36 h; [b] 48 h.

1.2.3 Substrate Scope of Aryl Chlorides in Palladium Catalyzed α-Arylation of Methyl Phenyl Sulfoxide (1.1a)

Aryl chlorides are known to be more challenging substrates than aryl bromides for a variety of cross-coupling reactions.[15] When we employed aryl chlorides under our optimized conditions for aryl bromides, only trace products were observed. We suspected catalyst activation might be problematic and turned to Buchwald-type second generation catalysts.[16] Thus, addition of **1.L2** to the palladium dimer (Scheme 1-5) followed by 0.33 mmol H_2O as additive[17] resulted in an active catalyst toward aryl chlorides (Scheme 1-5). As shown in Scheme 1-5, sulfoxide **1.3a** was isolated using **1.1a** and chlorobenzene (**1.2a'**) in 69% yield. Electron-donating (**1.3b**, **1.3c**) and electron-withdrawing groups (**1.3d**) were well tolerated when the corresponding aryl chlorides were used, as well as 1-naphthyl- (**1.2g'**) and *meta*-substituted aryl chlorides (**1.2f'**, **1.2i'**). Unfortunately, heterocyclic halides were not viable substrates under these conditions.

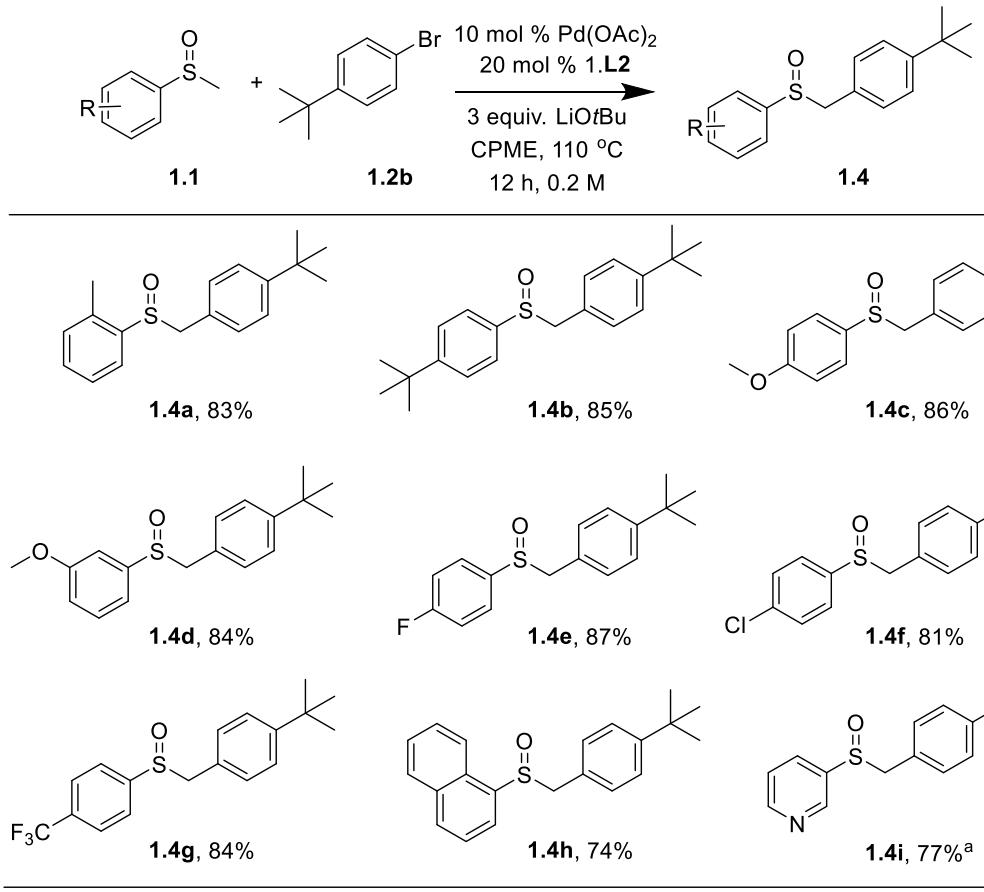
Scheme 1-5. Substrate scope of aryl chlorides in Pd-catalyzed α-arylation of unactivated sulfoxides.



1.2.4 Substrate Scope of Aryl Methyl Sulfoxides in Palladium Catalyzed α-Arylation with 4-*tert*-Butyl Bromobenzene (1.2b)

We then turned our attention to the substrate scope of aryl methyl sulfoxides using 4-*tert*-butyl bromobenzene (**1.2b**) as the coupling partner (Scheme 1-6). Electron-donating (**1.4b**, **1.4c**) and withdrawing groups (**1.4e**, **1.4f**, **1.4g**), *meta*-methoxy (**1.4f**), and *ortho*-methyl (**1.4a**) all led to good yields under our optimized conditions for aryl bromides (81–87%). In addition, methyl 1-naphthyl sulfoxide furnished product **1.4h** in 74% yield. Unfortunately, no product was isolated from 2-pyridyl or 2-pyrimidyl methyl sulfoxide, possibly due to chelation of nitrogen and sulfur or oxygen to palladium. Based on this hypothesis, we examined 3-pyridyl methyl sulfoxide and observed the generation of **1.4i** (77%), a key intermediate in an anti-virus compound.[18]

Scheme 1-6. Substrate scope of aryl methyl sulfoxides in Pd-catalyzed α-arylation of unactivated sulfoxides.

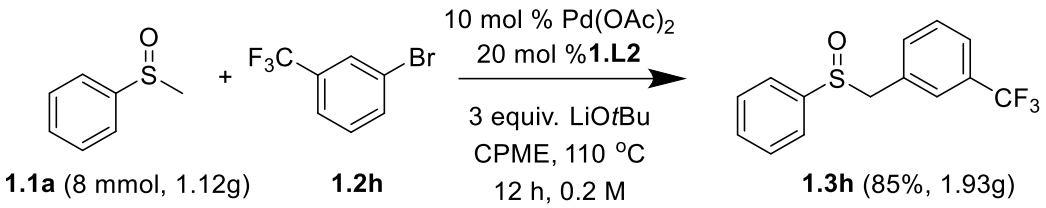


[a] 90 °C, 48 h.

1.2.5 Gram Scale Synthesis of 1.3h and Expansion of α-Arylation to Benzyl Phenyl Sulfoxide and Alkyl Methyl Sulfoxides

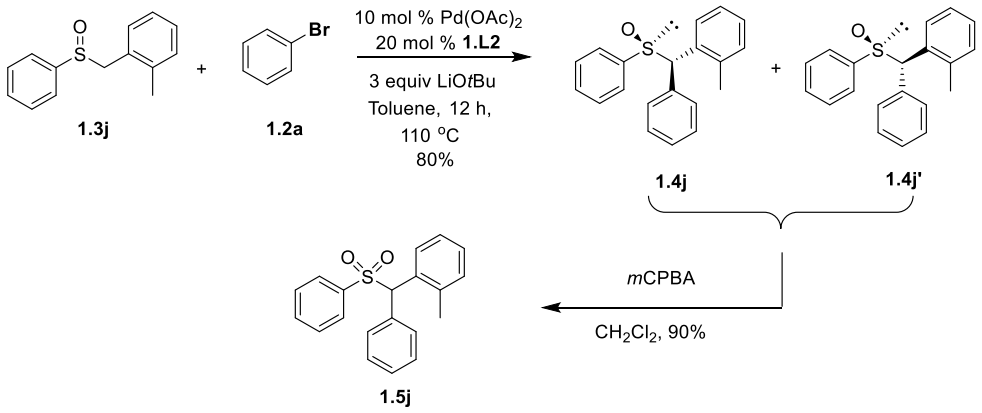
To demonstrate the potential application of our α-arylation in future synthesis, we tested the scalability of our protocol. When the DCCP with **1.1a** was scaled to 8 mmol (1.12 g) with 3-bromo trifluoromethyl benzene (**1.2h**), the product **1.3h** was isolated in 85% yield (Scheme 1-7). Sulfoxide **1.3h** could be used as the key intermediate in

the synthesis of an anti-cancer agent.[1d]



Scheme 1-7. Gram scale synthesis of **3h** via Pd-catalyzed α-arylation of sulfoxides.

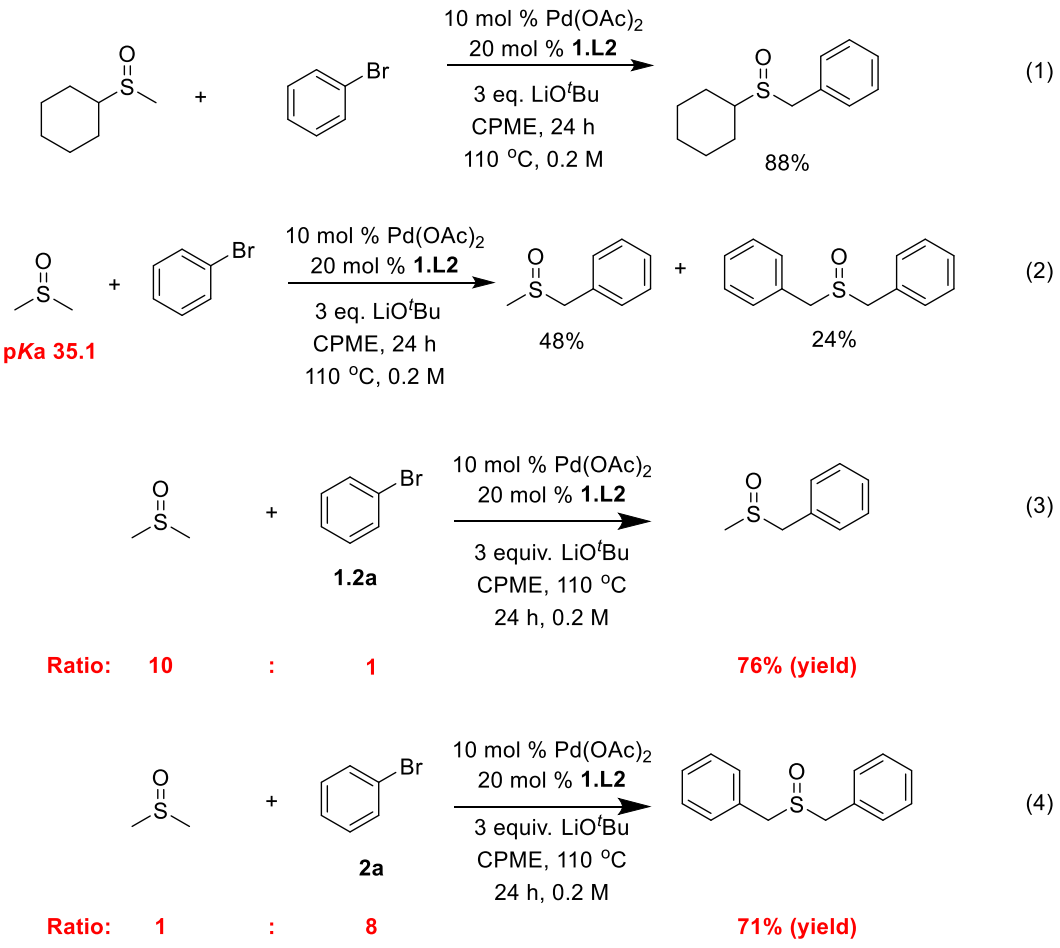
Coupling of sulfoxides with substituents other than methyl may give rise to diastereomers. As anticipated, cross-coupling of benzyl sulfoxides **1.3j** led to formation of a mixture of diastereomers in a 1:1.3 ratio. Unfortunately, we were unable to separate the diastereomers by column chromatography. The mixture of sulfoxides was therefore oxidized to sulfone **1.5j** in 90% yield (Scheme 1-8).[19]



Scheme 1-8. α-Arylation of **1.3j** with bromobenzene (**1.2a**), and subsequent oxidation to sulfone (**1.5j**).

Alkyl methyl sulfoxides are less acidic than aryl methyl sulfoxides and represent a greater challenge. As shown in Scheme 1-9, cyclohexyl methyl sulfoxide

underwent DCCP with **1.2a** to give the desired product in 88% yield after 24 h (Eq. 1). Interestingly, dimethyl sulfoxide (DMSO), a common organic solvent with p*K*a 35.1,[10a] could be utilized to prepare benzyl sulfoxides. Under the same condition as cyclohexyl methyl sulfoxide, mono- and bis-arylated products were obtained with DMSO and **1.2a** in 48% and 24% yield, respectively (Eq. 2). To control the selectivity, we adjusted the stoichiometry and optimized the reaction conditions for DMSO. Ultimately, we successfully generated either the mono- or dibenzylated products in 76% and 71% isolated yield when the ratio of DMSO to **1.2a** was 10:1 or 1:8, respectively (Eqs. 3&4).



Scheme 1-9. α-Arylation of alkyl methyl sulfoxides.

1.3 Conclusion

In summary, we have developed the first direct alpha-arylation of unactivated alkyl and aryl methyl sulfoxides with aryl bromides. Aryl chlorides also participate in the reaction catalyzed by *in situ* formation of a Buchwald 2nd generation-type pre-catalyst in the presence of H_2O as additive. The palladium catalyzed arylation proceeds efficiently in the presence of Kwong's indole-based phosphine and produced benzyl sulfoxides in good to excellent yields. Reversible deprotonation of the weakly acidic alpha protons of sulfoxides (with pK_as as high as 35) was achieved using LiO^{t}Bu. This direct arylation method provides a novel synthetic route to generate sulfoxides, an important class of bioactive compounds. We are currently exploring the mechanism and application of this chemistry to the synthesis of novel ligands. Expanding the substrates scope to heterocyclic halides by an additive strategy developed by our group[13b] is also under investigation.

1.4 Experimental Section

General Methods: All reactions were carried out under dry nitrogen. Anhydrous cyclopentyl methyl ether **(**CPME), dioxane, dichloroethane, and 2-MeTHF were purchased from Sigma-Aldrich and directly used without further purification. Toluene and THF were dried through activated alumina columns. Unless otherwise stated, reagents were commercially available and used as purchased without further

purification. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with iodine. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were taken with KBr plates with a Perkin-Elmer Spectrum 1600 Series spectrometer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and were uncorrected.

Preparation of sulfoxides: Sulfoxides were prepared according to literature procedures.[20,21]

Preparation of Pd Dimer for 2nd Generation Pre-catalyst: Palladium dimer for 2nd generation pre-catalyst was prepared according to the literature procedures.[16]

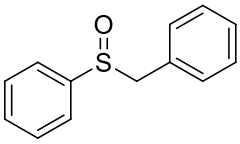
Procedure and Characterization for the Pd Catalyzed α-Arylation of Sulfoxides.

General Procedure A for catalysis: To an oven-dried microwave vial equipped with a stirbar was added $Pd(OAc)_2$ (4.48 mg, 0.02 mmol) and ligand **1.L2** (16.3 mg, 0.04

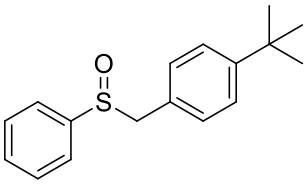
mmol) under a nitrogen atmosphere followed by 1.0 mL of dry CPME. After the catalyst/ligand solution was stirred for about 2 h at 24 ℃, LiO^{t}Bu (48.3 mg, 0.60 mmol, 3 equiv) was added to the reaction vial followed by methyl phenyl sulfoxide (24 mg, 0.20 mmol, 1.0 equiv). The microwave vial was sealed and 4-*tert*-butyl bromobenzene (79.2 μL, 0.40 mmol, 2.0 equiv) was added by syringe under a nitrogen atmosphere. Note that if the methyl sulfoxide or aryl bromide is a solid, it was added to the reaction vial before the LiO^{t}Bu. The reaction mixture was heated to 110 ℃ in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 10:1 dichloromethane:methanol (5.0 mL). The solvent was removed under reduced pressure to yield a viscous oil. The residue was purified by flash chromatography as outlined below.

General Procedure B for catalysis: To an oven-dried microwave vial equipped with a stirbar was added Pd dimer (3.10 mg, 0.01 mmol) and ligand **1.L2** (16.3 mg, 0.04 mmol) under a nitrogen atmosphere followed by 1.0 mL of dry THF. After the catalyst/ligand solution was stirred for about 2.5 h at 24 ℃, the solvent was removed *in vacuo* inside the glovebox. Dry toluene (1.0 mL) was added to the reaction vial followed by LiO^{t}Bu (48.3 mg, 0.60 mmol, 3 equiv) and methyl phenyl sulfoxide (24 mg, 0.20 mmol, 1.0 equiv). The microwave vial was sealed and 4-*tert*-butyl bromobenzene (79.2 μL, 0.40 mmol, 2.0 equiv) and H_2O (3.3 mmol, 6 μL, 1.66 equiv) were added by syringe through the rubber septum under nitrogen atmosphere. Note that if the methyl sulfoxide or aryl bromide is a solid, it was added to the reaction vial

before the LiO^tBu. The reaction mixture was heated to 110 ℃ in an oil bath and stirred for 24 h. The sealed vial was cooled, opened to air, and the reaction mixture was passed through a short pad of silica gel. The pad was then rinsed with 10:1 dichloromethane:methanol (5.0 mL). The resulting solution was subjected to reduced pressure to remove the volatile materials and yielded a viscous oil. The residue was purified by flash chromatography as outlined below.

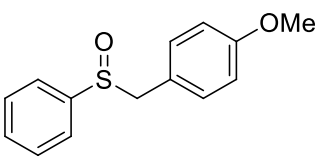


(Benzylsulfinyl)benzene (1.3a): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and bromobenzene (**1.2a**) (42.4 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (41.0 mg, 95% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

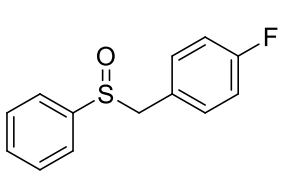


1-(*tert*-Butyl)-4-((phenylsulfinyl)methyl)benzene (1.3b): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (50.6 mg, 93% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 103–105 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 7.40 (m, 5H), 7.28 (d, *J* = 8 Hz, 2H), 6.82 (d, *J* = 8 Hz, 2H), 4.05 (d, *J* = 12.5 Hz, 1H), 3.96 (d, *J* = 12.5 Hz, 1H), 1.29 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 151.4, 143.1, 131.1,

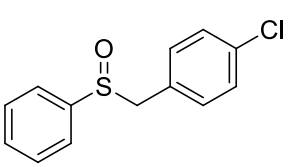
130.0, 128.8, 126.2, 125.4, 124.4, 63.5, 34.6, 31.2 ppm; IR (thin film): 3036, 2957, 2903, 1655, 1440, 1083, 1035, 833, 739, 688 cm^{-1}; HRMS calculated for $C_{17}H_{21}OS$ 273.1313, found 273.1318 $[M+H]^+$.



1-Methoxy-4-((phenylsulfinyl)methyl)benzene (1.3c): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-bromoanisole (**1.2c**) (50.0 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (40.8 mg, 83% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[23]

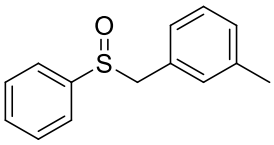


1-Fluoro-4-((phenylsulfinyl)methyl)benzene (1.3d): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 1-bromo-4-fluorobenzene (**1.2d**) (43.9 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (39.8 mg, 85% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

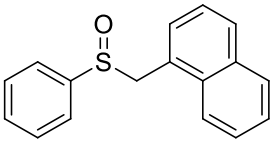


1-Chloro-4-((phenylsulfinyl)methyl)benzene (1.3e): The reaction was performed following General Procedure A with **1.1a** (14 mg, 0.10 mmol), LiO^tBu (24 mg, 0.30 mmol) and 1-bromo-4-chlorobenzene (**1.2e**) (38.3 μL, 0.20 mmol), 1.0 mL CPME, 0.1 M concentration. The crude product was purified by flash chromatography on silica gel

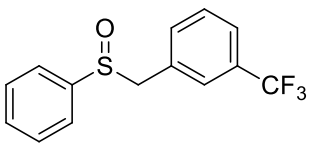
(eluted with EtOAc:hexanes = 1:10) to give the product (40.6 mg, 81% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]



1-Methyl-3-((phenylsulfinyl)methyl)benzene (1.3f): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 3-bromotoluene (**1.2f**) (48.5 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (39.6 mg, 86% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

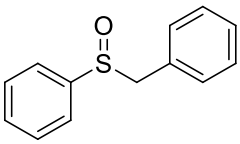


1-((Phenylsulfinyl)methyl)naphthalene (1.3g): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 1-bromonaphthalene (**1.2g**) (55.9 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (45.2 mg, 85% yield) as a white solid. R_f = 0.75 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

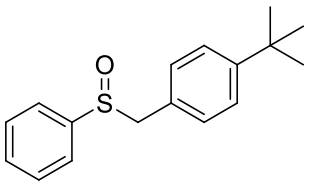


1-((Phenylsulfinyl)methyl)-3-(trifluoromethyl)benzene (1.3h): The reaction was performed following General Procedure A with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 3-bromobenzotrifluoride (**1.2h**) (55.8 μL, 0.40 mmol), 48 h. The crude product was purified by flash chromatography on silica gel (eluted with

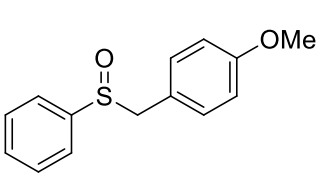
EtOAc:hexanes = 1:10) to give the product (47.1 mg, 83% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[24]



(Benzylsulfinyl)benzene (1.3a) (from chlorobenzene): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and chlorobenzene (**1.2a'**) (40.5 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (29.8 mg, 69% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

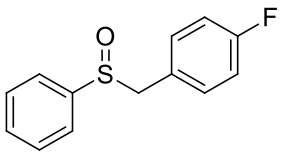


1-(*tert*-Butyl)-4-((phenylsulfinyl)methyl)benzene (1.3b) (from 4-*tert*-butyl chlorobenzene): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-*tert*-butyl chlorobenzene (**1.2b'**) (67.0 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (39.2 mg, 72% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3).

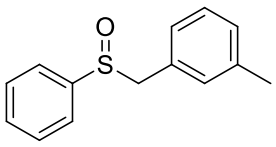


1-Methoxy-4-((phenylsulfinyl)methyl)benzene (1.3c) (from 4-chloroanisole): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-chloroanisole (**1.2c'**) (49.0 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with

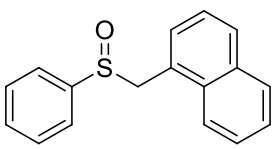
EtOAc:hexanes = 1:10) to give the product (33.4 mg, 83% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[23]



1-Fluoro-4-((phenylsulfinyl)methyl)benzene (1.3d) (from 1-chloro-4-fluorobenzene): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol), and 1-chloro-4-fluorobenzene (**1.2d'**) (42.6 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (37.0 mg, 79% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

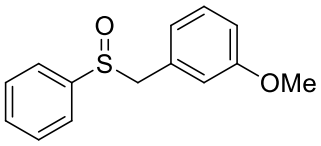


1-Methyl-3-((phenylsulfinyl)methyl)benzene (1.3f) (from 3-chlorotoluene): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 3-chlorotoluene (**1.2f'**) (47.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (35.0 mg, 76% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

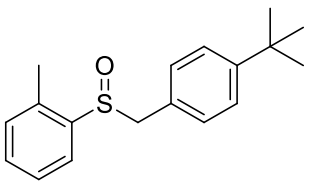


1-((Phenylsulfinyl)methyl)naphthalene (1.3g) (from 1-chloronaphthalene): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and

1-chloronaphthalene (**1.2g'**) (54.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (32.4 mg, 61% yield) as a white solid. R_f = 0.75 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[22]

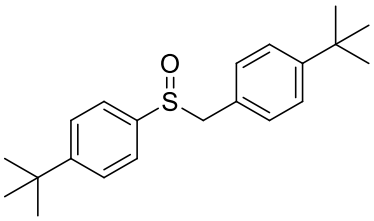


1-Methoxyl-3-((phenylsulfinyl)methyl)benzene (1.3j): The reaction was performed following General Procedure B with **1.1a** (28 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 3-chloroanisole (**1.2g'**) (49.0 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (37.4 mg, 76% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[25]

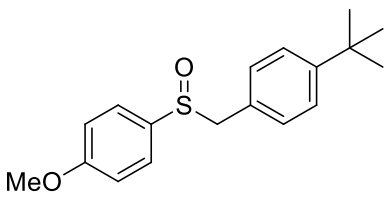


1-((4-(*tert*-Butyl)benzyl)sulfinyl)-2-methylbenzene (1.4a): The reaction was performed following General Procedure A with 1-methyl-2-(methylsulfinyl)benzene (30.8 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (47.5 mg, 85% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 113–115 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 5.5, 2 Hz, 1H), 7.36 (dd, *J* = 6, 3 Hz, 2H), 7.26 (d, *J* = 3 Hz, 2H), 7.11(dd, *J* = 5.5, 2 Hz, 1H), 6.94 (d, *J* = 6 Hz, 2H), 4.05 (d, *J* = 12.5 Hz, 1H), 3.96 (d, *J* = 12.5 Hz, 1H), 2.06 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 151.4, 141.6, 135.5, 130.7, 130.1, 129.9, 127.0, 126.3, 125.3, 124.1

ppm; IR (thin film): 3046, 2956, 2903, 1585, 1457, 1060, 1028, 830, 753, 746 cm^{-1}; HRMS calculated for $C_{18}H_{23}OS$ 287.1470, found 287.1476 $[M+H]^+$.

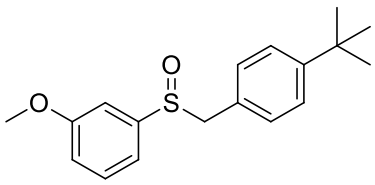


1-(*tert*-Butyl)-4-((4-(*tert*-butyl)benzyl)sulfinyl)benzene (1.4b): The reaction was performed following General Procedure A with 1-(*tert*-butyl)-4-(methylsulfinyl)benzene (39.2 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (55.8 mg, 85% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 126–131 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 6.98 (d, *J* = 8 Hz, 2H), 4.03 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 1.33 (s, 9H), 1.29 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 154.7, 151.2, 140.0 129.9, 126.7, 125.8, 125.4, 124.1, 63.7, 34.9, 34.5, 31.2, 31.1 ppm; IR (thin film): 2960, 2867, 1650, 1363, 1267, 1080, 1040, 1011, 842 cm^{-1}; HRMS calculated for $C_{21}H_{29}OS$ 329.1939, found 329.1940 $[M+H]^+$.

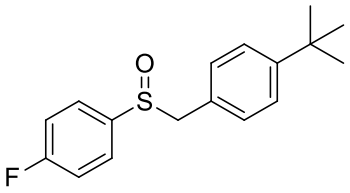


1-(*tert*-Butyl)-4-(((4-methoxyphenyl)sulfinyl)methyl)benzene (1.4c): The reaction was performed following General Procedure A with 1-methoxy-4-(methylsulfinyl)benzene (34 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4- *tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with

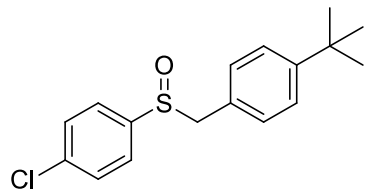
EtOAc:hexanes = 1:10) to give the product (51.9 mg, 86% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 82–85 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, *J* = 6.5 Hz, 2H), 7.26 (d, *J* = 6.5 Hz, 2H), 7.01 – 6.90 (m, 4H), 4.05 (d, *J* = 12.5 Hz, 1H), 3.92 (d, *J* = 12.5 Hz, 1H), 3.86 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.9, 151.2, 134.0, 130.0, 126.4, 126.2, 125.4, 114.3, 63.6, 55.4, 34.5, 31.2 ppm; IR (thin film): 2962, 1594, 1496, 1463, 1304, 1252, 1086, 1044, 830 cm^{-1}; HRMS calculated for $C_{18}H_{23}O_2S$ 303.1419, found 303.1425 $[M+H]^+$.



1-((4-(*tert*-Butyl)benzyl)sulfinyl)-3-methoxybenzene (1.4d): The reaction was performed following General Procedure A with 1-methoxy-3-(methylsulfinyl)benzene (34 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (50.7 mg, 84% yield) as a pale yellow solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 80–84 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 3H), 6.99 – 6.87 (m, 4H), 6.86 (s, 1H), 4.02 (d, *J* = 12.5 Hz, 1H), 3.97 (d, *J* = 12.5 Hz, 1H), 3.71 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.9, 151.3, 144.3, 130.0, 129.6, 126.1, 125.3, 118.0, 116.3, 108.3, 63.2, 55.4, 34.5, 31.2 ppm; IR (thin film): 2961, 1593, 1480, 1423, 1363, 1283, 1249, 1042, 837, 783 cm^{-1}; HRMS calculated for $C_{18}H_{23}O_2S$ 303.1419, found 303.1425 $[M+H]^+$.

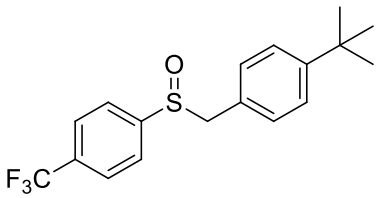


1-(*tert*-Butyl)-4-(((4-fluorophenyl)sulfinyl)methyl)benzene (1.4e): The reaction was performed following General Procedure A with 1-fluoro-4-(methylsulfinyl)benzene (31.6 mg, 0.20 mmol), LiO^{t}Bu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (50.5 mg, 87% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 125–127 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.35 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.11 (t, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 4.07 (d, *J* = 12.5 Hz, 1H), 3.94 (d, *J* = 12.5 Hz, 1H), 1.29 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.4 (d, $J^1_{C\text{-}F}$ = 250 Hz), 151.5, 138.3, 130.0, 126.7 (d, $J^3_{C\text{-}F}$ = 8.8 Hz) 125.8, 125.5, 116.1 (d, $J^2_{C\text{-}F}$ = 22 Hz), 63.4 , 34.6, 31.2 ppm; IR (thin film): 2961, 1489, 1458, 1366, 1218, 1060, 1028, 830, 754 cm^{-1}; HRMS calculated for $C_{17}H_{20}OSF$ 291.1219, found 291.1223 $[M+H]^+$.

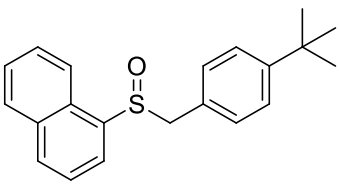


1-(*tert*-Butyl)-4-(((4-chlorophenyl)sulfinyl)methyl)benzene (1.4f): The reaction was performed following General Procedure A with 1-chloro-4-(methylsulfinyl)benzene (34.9 mg, 0.20 mmol), LiO^{t}Bu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (49.7 mg, 81% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 147–151 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ

7.39 (d, *J* = 8.5 Hz, 2H), 7.30 (dd, *J* = 8.5, 8 Hz, 2H), 6.94 (d, *J* = 8 Hz, 2H), 4.06 (d, *J* = 12.5 Hz, 1H), 3.94 (d, *J* = 12.5 Hz, 1H), 1.29 (s, 9H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 151.8, 141.5, 137.2, 130.0, 129.0, 125.8, 125.7, 125.5, 63.3, 34.5, 31.2 ppm; IR (thin film): 3050, 2958, 1474, 1388, 1266, 1033, 1008, 819 cm^{-1}; HRMS calculated for $C_{17}H_{19}OSClNa$ 329.0743, found 329.0747 $[M+Na]^+$.

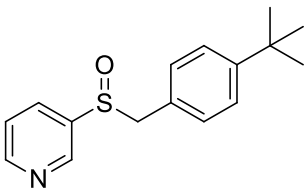


1-(*tert*-Butyl)-4-(((4-(trifluoromethyl)phenyl)sulfinyl)methyl)benzene (1.4g): The reaction was performed following General Procedure A with 1-(methylsulfinyl)-4-(trifluoromethyl)benzene (41.6 mg, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (57.1 mg, 84% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 124-–128 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 4.08 (d, *J* = 12.5 Hz, 1H), 3.99 (d, *J* = 12.5 Hz, 1H), 1.30 (s, 9H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 151.8, 147.5, 133.1 (q, $J^2_{C\text{-}F}$ = 33 Hz), 130.0, 125.7 (q, $J^3_{C\text{-}F}$ = 3.7 Hz), 125.6, 125.5, 124.9, 123.5(q, $J^1_{C\text{-}F}$ = 270.9 Hz), 63.3, 34.6, 31.2 ppm; IR (thin film): 2967, 1400, 1323, 1160, 1126, 1103, 1039, 831 cm^{-1}; HRMS calculated for $C_{18}H_{19}OSF_3Na$ 363.1006, found 363.1022 $[M+Na]^+$.



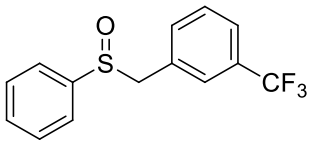
1-((4-(*tert*-Butyl)benzyl)sulfinyl)naphthalene (1.4h): The reaction was performed following General Procedure A with 1-(methylsulfinyl)naphthalene (38.0 mg, 0.20

mmol), LiO^{t}Bu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (47.7 mg, 74% yield) as a white solid. R_f = 0.7 (hexanes:EtOAc = 2:3); m.p. = 107–110 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 12, 3.5 Hz, 2H), 7.85 (dd, *J* = 17.5, 8 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.17 (d, *J* = 12.5 Hz, 1H), 4.06 (d, *J* = 12.5 Hz, 1H), 1.24 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 151.3, 139.0, 133.1, 130.0, 129.3, 128.8, 127.0, 126.5, 126.4, 125.4, 125.3, 123.4, 121.5, 62.1, 34.5, 31.2 ppm; IR (thin film): 2957, 1504, 1363, 1107, 1050, 799, 769 cm^{-1}; HRMS calculated for $C_{21}H_{22}OSNa$ 345.1289, found 345.1288 $[M+Na]^+$.

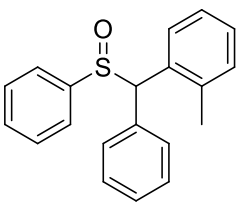


3-((4-(*tert*-Butyl)benzyl)sulfinyl)pyridine (1.4i): The reaction was performed following General Procedure A with 3-(methylsulfinyl)pyridine (28.2 mg, 0.20 mmol), LiO^{t}Bu (48 mg, 0.60 mmol) and 4-*tert*-butyl bromobenzene (**1.2b**) (79.2 μL, 0.40 mmol), 48 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (42.0 mg, 77% yield) as a white solid. R_f = 0.6 (hexanes:EtOAc = 2:3); m.p. = 71–75 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67 (br s, 1H), 8.45 (br s, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.36 – 7.34 (m, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.12 (d, *J* = 12.5 Hz, 1H), 4.02 (d, *J* = 12.5 Hz, 1H), 1.27 (s, 9H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 152.0, 151.9, 146.0, 139.5, 132.4, 130.1, 125.6, 125.1, 123.8, 63.1, 34.6, 31.2 ppm; IR (thin film): 3051, 2962, 1570, 1515, 1465, 1412, 1269, 1192, 1084, 1051, 838, 705 cm^{-1}; HRMS

calculated for $C_{16}H_{20}OSN$ 274.1266, found 274.1254 $[M+H]^+$.

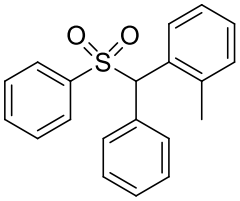


1-((Phenylsulfinyl)methyl)-3-(trifluoromethyl)benzene (1.3h) (8 mmol scale): To an oven-dried Schlenk flask equipped with a stirbar was added $Pd(OAc)_2$ (180 mg, 0.4 mmol) and ligand **1.L2** (403.5 mg, 0.8 mmol) under a nitrogen atmosphere followed by addition of 40.0 mL of dry CPME via syringe. The catalyst/ligand solution was stirred for 2 h at 24 ℃. LiO^tBu (1.92 mg, 24 mmol, 3 equiv) was added to the reaction followed by methyl phenyl sulfoxide (1.12 g, 8 mmol, 1.0 equiv). The reaction flask was equipped with an air condenser and put under nitrogen. 3-Bromobenzotrifluoride (**1.2h**) (16 mL, 16 mmol, 2.0 equiv) was added via syringe under a nitrogen atmosphere. The reaction was heated to 110 ℃ and stirred for 24 h. A large amount of precipitate was observed after the reaction was complete, which was presumably LiBr. The reaction mixture was passed through a short pad of silica gel and eluted with 10:1 dichloromethane:methanol. The volatile materials were removed under reduced pressure to yield a viscous oil. The residue was purified by flash chromatography (EtOAc:hexanes = 1:10) to give the product (1.93 g, 85% yield) as a white solid. The spectroscopic data match the previously reported data.[24]

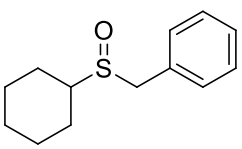


1-Methyl-2-(phenyl(phenylsulfinyl)methyl)benzene (1.4j and 1.4j'): The reaction was performed following General Procedure A with 1-methyl-2-((phenylsulfinyl)methyl)benzene (**1.3j**) (92mg, 0.40 mmol), bromobenzene (**1.2a**) (21.2 μL, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol), and toluene (1.0 mL) as solvent, 12 h. The crude product was eluted by flash

chromatography on silica with 100% hexanes to obtain **1.4j** and **1.4j'** (49.0 mg, 80%). The mixture was used directly for the following oxidationstep without further purification. The d.r. of the products (1:1.3) was determined by ^{1}H NMR.

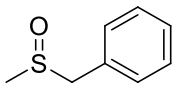


Oxidation of Sulfoxides (1.4j and 1.4j') to Sulfone (1-Methyl-2-(phenyl(phenylsulfonyl)methyl)benzene (1.5j)): The mixture of 1-methyl-2-(phenyl(phenylsulfinyl)methyl)benzene (**1.4j** and **1.4j'**) (49.0 mg, 0.16 mmol) and *m*CPBA (39.4 mg, 70% *w/w*, 0.16 mmol) was added into a vial, fitted with a stir bar, and dissolved in 1.0 mL CH_2Cl_2. The reaction was stirred overnight, and volatile materials removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with 100% hexanes) to give the product (46.4 mg, 90% yield) as a white solid. R_f = 0.5 (hexanes:EtOAc = 4:1); m.p. = 107–110 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 (m, 2H), 7.33 (m, 4H), 7.18 (t, *J* = 7 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 5.59 (s, 1H), 2.01 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 138.6, 136.8, 133.5, 132.7, 131.8, 130.7, 130.2, 129.0, 128.9, 128.6, 128.6, 128.5, 128.4, 126.4, 71.3 ppm; IR (thin film): 1494, 1447, 1318, 1308, 1287, 1146, 1084, 757, 721, 688, 586 cm^{-1}; HRMS calculated for $C_{20}H_{18}O_2SNa$ 345.0925, found 345.0935 $[M+Na]^+$.

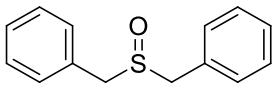


((Cyclohexylsulfinyl)methyl)bezene (1.4k): The reaction was performed following General Procedure A with (methylsulfinyl)cyclohexane (29.2 mg, 0.20 mmol), LiO^tBu (48

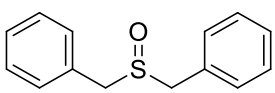
mg, 0.60 mmol) and bromobenzene (**1.2a**) (42.4 μL, 0.40 mmol). The reaction was heated for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with 100% EtOAc) to give the product (39.1 mg, 88% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[26]



((Methylsulfinyl)methyl)benzene(1.4l): The reaction was performed following General Procedure A with dimethyl sulfoxide (14.2 μL, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and bromobenzene (**1.2a**) (42.4 μL, 0.40 mmol). The reaction was heated for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with 100% EtOAc) to give the product (14.8 mg, 48% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[27]



(Sulfinylbis(methylene))dibenzene (1.4l'): The reaction was performed following General Procedure A with dimethyl sulfoxide (14.2 μL, 0.20 mmol), LiO^tBu (48 mg, 0.60 mmol) and bromobenzene (**1.2a**) (42.4 μL, 0.40 mmol). The reaction was heated for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with 100% EtOAc) to give the product (11.0 mg, 24% yield) as a white solid. R_f = 0.6 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[27]



(Sulfinylbis(methylene))dibenzene (1.4l'): The reaction was performed following General Procedure A with dimethyl sulfoxide (14.2 μL, 0.20 mmol, 1 equiv.), LiO^tBu (48 mg, 0.60 mmol) and

bromobenzene (**1.2a**) 169.6 μL, 1.6 mmol, 8 equiv). The reaction was heated for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with 100% EtOAc) to give the product (32.5 mg, 71% yield) as a white solid. R_f = 0.6 (hexanes:EtOAc = 2:3). The spectroscopic data match the previously reported data.[27]

High-throughput Experimentation Screenings for Pd-Catalyzed Arylation of Sulfoxides

General Experimental Procedure (Exemplified by ligand screening):

Set up:

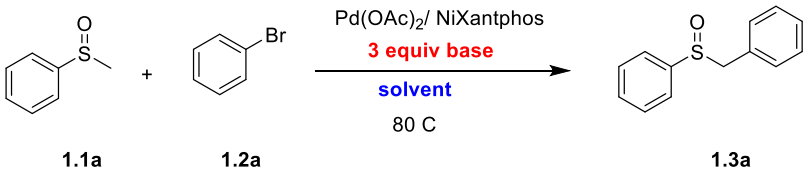
Experiments were set up inside a glovebox under a nitrogen atmosphere. A 96-well aluminum block containing 1 mL glass vials was predosed with $Pd(OAc)_2$ (1 μmol) and the phosphine ligands (2 μmol for monodentate ligands and 1 μmol for bidentate ligands) in THF. The solvent was removed to dryness using a GeneVac and LiO*t*Bu (30 μmol) in THF was added to the ligand/catalyst mixture. The solvent was removed on the GeneVac and a parylene stir bar was then added to each reaction vial. Methyl phenyl sulfoxide (10 μmol/reaction), bromobenzene (20 μmol) and 4,4′-di-*tert*-butylbiphenyl (1 μmol/reaction) (used as an internal standard to measure HPLC yields) were then dosed together into each reaction vial as a solution in CPME (100 μL, 0.1 M). The 96-well plate was then sealed and stirred for 18 h at 80 °C.

Work up:

Upon opening the plate to air, 500 μL of acetonitrile was added into each vial. The plate was covered again and the vials stirred for 10 min. to ensure good homogenization. Into a separate 96-well LC block was added 700 μL of acetonitrile,

followed by 40 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on an automated HPLC instrument for analysis.

Table 1-2. Base and solvent screening.



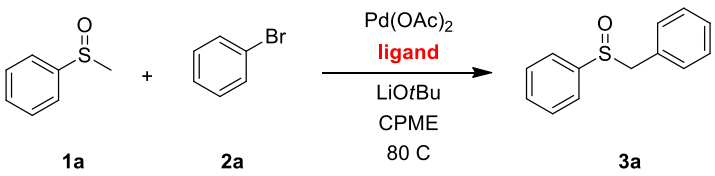
Bases: $KN(SiMe_3)_2$, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, KO*t*Bu, LiO*t*Bu, NaO*t*Bu.

Solvent: CPME, dioxane, THF, toluene.

Well	**Base**	**Solvent**	**Prod/IS**	**AY 3a (%)**
A01	LiO^tBu	CPME	2.77	40.5
B01		dioxane	1.93	28.1
C01		THF	0.07	1.0
D01		toluene	0.00	0.0
A02	NaO^tBu	CPME	0.04	0.5
B02		dioxane	0.00	0.0
C02		THF	1.93	28.1
D02		toluene	2.54	37.1

A03	KO^{t}Bu	CPME	0.90	13.2
B03		dioxane	0.00	0.0
C03		THF	0.18	2.6
D03		toluene	0.17	2.5
A04	$LiN(SiMe_3)_2$	CPME	2.28	33.3
B04		dioxane	1.21	17.7
C04		THF	0.14	2.0
D04		toluene	0.00	0.0
A05	$NaN(SiMe_3)_2$	CPME	0.00	0.0
B05		dioxane	0.00	0.0
C05		THF	2.57	37.5
D05		toluene	0.00	0.0
A06	$KN(SiMe_3)_2$	CPME	0.00	0.0
B06		dioxane	0.00	0.0
C06		THF	0.00	0.0
D06		toluene	0.14	2.1

Table 1-3. Ligand screening



Ligands:

	Ligand libraries
1	2-Di-t*ert*-butylphosphino-2',4',6'-triisopropylbiphenyl (*t*Bu-XPhos)
2	2-(Dicyclohexylphosphino)-2'-methylbiphenyl (MePhos)
3	2-(Di-*tert*-butylphosphino)-2'-methylbiphenyl (*t*Bu-MePhos)
4	2-(Dicyclohexylphosphino)biphenyl (Cy-JohnPhos)
5	2-Di-t-butylphoshino-2'-(*N*,*N*-dimethylamino)biphenyl (*t*Bu-DavePhos)
6	Racemic-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl
7	1-[2-[Bis(*tert*-butyl)phosphino]phenyl]-3,5-diphenyl-1H-pyrazole (TrippyPhos)
8	5-(Di-*tert*-butylphosphino)-1', 3', 5'-triphenyl-1'H-[1,4']bipyrazole (BippyPhos)
9	Dicyclohexyl-[2-(*o*-tolyl)indol-1-yl]phosphane
10	Di-*tert*-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine (cBRIDP [MoPhos])
11	Dicyclohexyl-(1-methyl-2,2-diphenyl-cyclopropyl)phosphane (Cy-cBRIDP)
12	Dicyclohexyl-(1-methyl-2,2-diphenyl-vinyl)phosphane (Cy-vBRIDP)
13	*N*-phenyl-2-(dicyclohexylphosphino)pyrrole (cataCXium PCy)
14	*N*-phenyl-2-(di-*tert*-butylphosphino)pyrrole (cataCXium PtB)
15	Dicyclohexyl-(1-phenylindol-2-yl)phosphane (cataCXium PInCy)
16	Di-*tert*-butyl-(1-phenylindol-2-yl)phosphane (cataCXium PIntB)
17	1-(2-Methoxylphenyl)-2-(dicyclohexylphosphino)pyrrole (cataCXium

	POMeCy)
18	Di-*tert*-butyl-[1-(2-methoxyphenyl)pyrrol-2-yl]phosphane (cataCXium POMetB)
19	1-(2,4,6-Trimethylphenyl)-2-(dicyclohexylphosphino)imidazole (cataCXium PICy)
20	Di-(2-pyridyl)(dicyclohexylphosphino)amine (cataCXium KCy)
21	Di-(2-pyridyl)(diphenylphosphino)amine (cataCXium KPh)
22	(9-Butylfluoren-9-yl)-dicyclohexyl-phosphonium tetrafluoroborate (cataCXium FBu)
23	Dicyclohexyl-(9-phenethylfluoren-9-yl)phosphonium tetrafluoroborate (cataCXium FPrPh)
24	(9-Benzylfluoren-9-yl)-dicyclohexyl-phosphane; trifluoroborane; hydrofluoride (cataCXium FBn)
25	Trimethylphosphonium tetrafluoroborate
26	Triethylphosphonium tetrafluoroborate
27	Triisopropylphosphonium tetrafluoroborate
28	Tricyclohexylphosphonium tetrafluoroborate
29	Tribenzylphosphine
30	Di-*tert*-butylmethylphosphonium tetrafluoroborate
31	*tert*-Butyldicyclohexylphosphine
32	Di-*tert*-butylcyclohexylphosphine

33	Benzyldi-1-adamantylphosphine (cataCXium ABn)
34	Di-*tert*-butylneopentylphosphonium tetrafluoroborate
35	(Z)-1-*tert*-butyl-2,3,6,7-tetrahydro-1H-phosphepinium tetrafluoroborate (Ellman ligand)
36	1,3,5-Triaza-7-phosphaadamantane
37	Di-*tert*-butylphenylphosphonium tetrafluoroborate
38	Dicyclohexylphenylphosphine
39	(*o*-Toyl)dicyclohexylphosphine
40	Dicyclohexyl-(2,4,6-trimethylphenyl)phosphine
41	Dicyclohexyl-(2,6-diisopropylphenyl)phosphine
42	1-Dicyclohexylphosphino-4-dimethylaminobenzene
43	1,3,5,7-Tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphatricyclo[3.3.1.13,7]decane
44	2-(Dicyclohexylphosphino)benzophenone
45	2'-(Dicyclohexylphosphino)acetophenone ethylene ketal
46	1-Di-*iso*-propylphosphino-2-(*N*,*N*-dimethylamino)-1H-indene
47	11-Dicyclohexylphosphino-12-phenyl-9,10-ethenoanthracene (KitPhos)
48	11-Dicyclohexylphosphino-12-(2-methoxyphenyl)-9,10-ethenoanthracene (*o*-Meo-Kitphos)
49	Triphenylphosphine
50	Tri-*o*-tolylphosphine

51	Trimesitylphosphine
52	Tri(2-furyl)phosphine
53	Tris(2-methoxyphenyl)phosphine
54	Tris(4-methoxyphenyl)phosphine
55	Tris(2,4,6-trimethoxyphenyl)phosphine
56	Tris(4-fluorophenyl)phosphine
57	Tris(pentafluorophenyl)phosphine
58	Tris[3,5-bis(trifluoromethyl)phenyl]phosphine
59	Tri(1-naphthyl)phosphine
60	1,2-Bis(diphenylphosphino)ethane monoxide
61	Cyclohexyldiphenylphosphine
62	*tert*-Butyldiphenylphosphine
63	Benzyldiphenylphosphine
64	4-(Dimethylamino)phenyldiphenylphosphine
65	Diphenyl-2-pyridylphosphine
66	2-(1,1-Dimethylpropyl)-6-(diphenylphosphino)pyridine (AlpyPhos)
67	2-(Diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine (ArpyPhos)
68	1-Diphenylphosphino-2-(*N*,*N*-dimethylamino)-1H-indene
69	2-(Diphenylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (Ph-DavePhos)
70	Tris(2,4-di-*tert*-butylphenyl)phosphate
71	(1,1'-Ferrocenediyl)phenylphosphine (1,1'-(PhP)-ferrocene)

72	1,4-Bis(diphenylphosphino)butane monoxide
73	Bis(diphenylphosphino)methane
74	1,2-Bis(diphenylphosphino)ethane (dppe [diphos])
75	1,3-Bis(diphenylphosphino)propane (dppp)
76	1,4-Bis(diphenylphosphino)butane (dppb)
77	1,5-Bis(diphenylphosphino)pentane (dpppe)
78	1,8-Bis(diphenylphosphino)octane (dppo)
79	1,2-Bis(dipentafluorophenylphosphino)ethane
80	1,2-Bis(di-2-pyridylphosphino)ethane
81	1,2-Bis(diphenylphosphinomethyl)benzene
82	1,2-Bis(diphenylphosphino)benzene (dppbz)
83	1,8-Bis(diphenylphosphanyl)naphthalene
84	1,2,3,4-(Diphenylphosphinomethyl)cyclopentane (Tedicyp)
85	Bis(2-diphenylphosphinophenyl)ether (DPEPhos)
86	2,2'-Bis(diphenylphosphino)benzophenone (dpbp)
87	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (XantPhos)
88	4,6-Bis(diphenylphosphino)phenoxazine (NiXantPhos)
89	(*S*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ((*S*)-BINAP)
90	(R)-(+)-2,2'-bis(di-p-Tolylphosphino)-1,1'-binaphthyl ((R)-Tol-BINAP)
91	2,2'-Bis(diphenylphosphino)-1,1'-biphenyl (Biphep)
92	3,3'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro[2,2']binaphthalene

	hemichloroform adduct (Cy-Nu-Biphep)
93	6,6'-Bis(diphenylphosphino)-1,1',3,3'-tetrahydro[5,5']biisobenzofuran (Thf-Nu-Biphep)
94	Tetramethyl 6,6'-bis(diphenylphosphino)-1,1',3,3'-tetrahydro[5,5']biindenyl-2,2',2,2'-tetracarboxylate
95	2-(Diphenylphosphino)ethylamine
96	2-[2-(Diphenylphosphino)ethyl]pyridine
97	2-Dicyclohexylphosphino-2',4',6'-tri-*iso*-propyl-1,1'-biphenyl (XPhos)
98	2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (SPhos)
99	2-(Di-*tert*-butylphosphino)biphenyl (JohnPhos)
100	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (DavePhos)
101	2-Dicyclohexylphosphino-2',6'-di-*iso*-propoxy-1,1'-biphenyl (RuPhos)
102	2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (Me-4-*t*Bu-XPhos)
103	Dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (BrettPhos)
104	Butyldi-1-adamantylphosphine (cataCXium A)

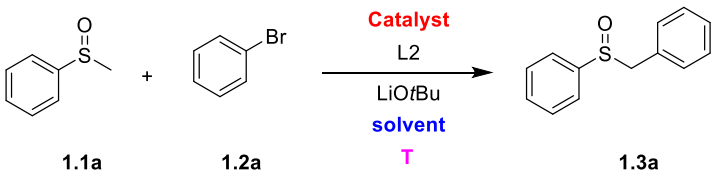
105	1,2,3,4,5-Pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (QPhos)
106	Tri-*tert*-butylphosphonium tetrafluoroborate
107	(4-(*N*,*N*-dimethylamino)phenyl)di-*tert*-butyl phosphine (AmPhos)
108	1,1'-Bis(di-*tert*-butylphosphino)ferrocene (dtbpf)
109	1,1'-Bis(diphenylphosphino)ferrocene (dppf)
110	1,1'-Bis(diisopropylphosphino)ferrocene (dippf)
111	(*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ((R)-BINAP)
112	(*R*)-(-)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine (JosiPhos SL-J009-1)

1 – 24: Monodentate dialkyl biaryl phosphine ligands; 25 – 48: Monodentate trialkyl and dialkylaryl phosphine ligands; 49 – 72: Monodentate triaryl and diarylalkylphosphine ligands; 73 – 96: Bidentate electron-poor phosphine ligands; 97 – 108: Monodentate phosphine ligands; 109 – 112: Bidentate and Monodentate Phosphine Ligands.

Ligand	**Prod/IS**	**Conversion (%)**
Cy-JohnPhos	1.33	70
Dicyclohexyl-[2-*o*-tolylindol-1-yl]phosphane	1.90	100
tert-Butyldicyclohexylphosphine	0.71	50
Di-*tert*-butylneopentylphosphonium tetrafluoroborate	1.11	100
2'-Dicyclohexylphosphino-acetophenone ethylene ketal	0.93	52
Ph-DavePhos	1.25	68
Dppf	1.07	100
R-BINAP	1.17	81
CataXCium PtB	0.95	79

No product was observed when using other ligands.

Table 1-4. Pd source, solvent and temperature screening



1:1.5

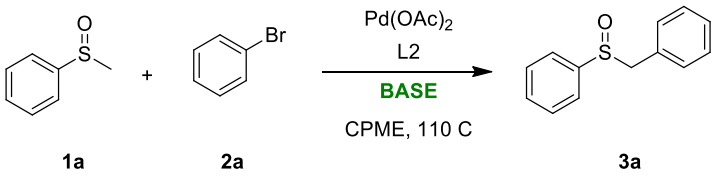
	110 °C

Well	**Catalyst**	**Solvent**	**Conversion (%)**	**AY 3a (%)**
A01	$Pd(OAc)_2$	CPME	83.9	79.5
A02	$[Pd(allyl)Cl]_2$	CPME	82.4	67.1
A03	$Pd(ACN)_2Cl_2$	CPME	83.6	74.9
A04	$Pd(COD)Cl_2$	CPME	82.2	78.1
A05	$Pd(PPh_3)_4$	CPME	100.0	71.3
A06	Pd_2dba_3	CPME	78.0	48.7
B01	$Pd(OAc)_2$	dioxane	100.0	44.8
B02	$[Pd(allyl)Cl]_2$	dioxane	100.0	47.4
B03	$Pd(ACN)_2Cl_2$	dioxane	100.0	46.5
B04	$Pd(COD)Cl_2$	dioxane	73.4	50.4
B05	$Pd(PPh_3)_4$	dioxane	100.0	59.3
B06	Pd_2dba_3	dioxane	71.6	30.1
C01	$Pd(OAc)_2$	THF	100.0	41.8
C02	$[Pd(allyl)Cl]_2$	THF	100.0	50.6
C03	$Pd(ACN)_2Cl_2$	THF	100.0	50.5
C04	$Pd(COD)Cl_2$	THF	100.0	51.3
C05	$Pd(PPh_3)_4$	THF	100.0	66.9
C06	Pd_2dba_3	THF	100.0	31.5
D01	$Pd(OAc)_2$	2-MeTHF	100.0	54.5

D02	$[Pd(allyl)Cl]_2$	2-MeTHF	100.0	45.3
D03	$Pd(ACN)_2Cl_2$	2-MeTHF	100.0	52.1
D04	$Pd(COD)Cl_2$	2-MeTHF	100.0	54.6
D05	$Pd(PPh_3)_4$	2-MeTHF	100.0	71.3
D06	Pd_2dba_3	2-MeTHF	100.0	31.1
	80 °C			
A01	$Pd(OAc)_2$	CPME	55.6	57.5
A02	$[Pd(allyl)Cl]_2$	CPME	77.6	65.7
A03	$Pd(ACN)_2Cl_2$	CPME	55.4	55.3
A04	$Pd(COD)Cl_2$	CPME	53.5	56.2
A05	$Pd(PPh_3)_4$	CPME	62.6	53.5
A06	Pd_2dba_3	CPME	39.9	28.4
B01	$Pd(OAc)_2$	dioxane	25.8	15.2
B02	$[Pd(allyl)Cl]_2$	dioxane	45.4	30.9
B03	$Pd(ACN)_2Cl_2$	dioxane	28.9	16.9
B04	$Pd(COD)Cl_2$	dioxane	33.2	22.8
B05	$Pd(PPh_3)_4$	dioxane	86.8	61.6
B06	Pd_2dba_3	dioxane	9.5	3.8
C01	$Pd(OAc)_2$	THF	50.4	34.7
C02	$[Pd(allyl)Cl]_2$	THF	100.0	65.8
C03	$Pd(ACN)_2Cl_2$	THF	100.0	58.1

C04	$Pd(COD)Cl_2$	THF	100.0	40.2
C05	$Pd(PPh_3)_4$	THF	100.0	64.1
C06	Pd_2dba_3	THF	43.1	22.4
D01	$Pd(OAc)_2$	2-MeTHF	100.0	69.9
D02	$[Pd(allyl)Cl]_2$	2-MeTHF	100.0	53.0
D03	$Pd(ACN)_2Cl_2$	2-MeTHF	100.0	61.3
D04	$Pd(COD)Cl_2$	2-MeTHF	100.0	64.3
D05	$Pd(PPh_3)_4$	2-MeTHF	100.0	67.3
D06	Pd_2dba_3	2-MeTHF	100.0	54.0

Table 1-5. Base and ratio **1a**:**2a** screening [28]



Well	**Base**	**Ratio 1a:2a**	**AY 3a (%)**
A01	LiO^tBu	1.5:1	74.2
B01		1:1.5	80.0
C01		2:1	81.4
D01		1:2	87.4

A02	NaO^tBu	1.5:1	3.5
B02		1:1.5	4.3
C02		2:1	3.5
D02		1:2	4.1
A03	KO^tBu	1.5:1	5.3
B03		1:1.5	5.4
C03		2:1	5.2
D03		1:2	4.6
A04	$LiN(SiMe_3)_2$	1.5:1	0.0
B04		1:1.5	0.0
C04		2:1	0.0
D04		1:2	0.0
A05	$NaN(SiMe_3)_2$	1.5:1	0.0
B05		1:1.5	0.0
C05		2:1	0.0
D05		1:2	0.0
A06	$KN(SiMe_3)_2$	1.5:1	0.0
B06		1:1.5	0.0
C06		2:1	0.0
D06		1:2	0.0

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Chapter 2 Diaryl Sulfoxides from Aryl Benzyl Sulfoxides: A Single Palladium Catalyzed Triple Relay Process

2.1 Introduction

2.1.1 Introduction to Sulfoxides

Sulfoxides are widely occurring in natural products,[1] synthetic bioactive compounds[2] and materials.[3] They are also very important structural motifs in marketed therapeutics, such as Nexium for heartburn and esophagitis[4a] and Provigil for narcolepsy (Figure 2-1).[4b] Furthermore, in recent years, sulfoxides have attracted attention as ligands in catalysis (Figure 2-2).[5] Two classic methods to generate diaryl sulfoxides are the oxidation of sulfides[6] and the nucleophilic substitution of electrophilic sulfinamides or sulfinate esters.[7] Despite the importance of sulfoxides, rapid syntheses of diversified diaryl sulfoxides remains challenging.

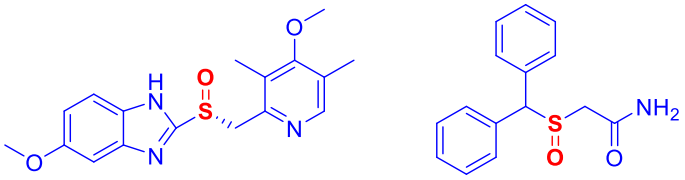


Figure 2-1. Representative sulfoxide-containing marketed therapeutics: Nexium and Provigil

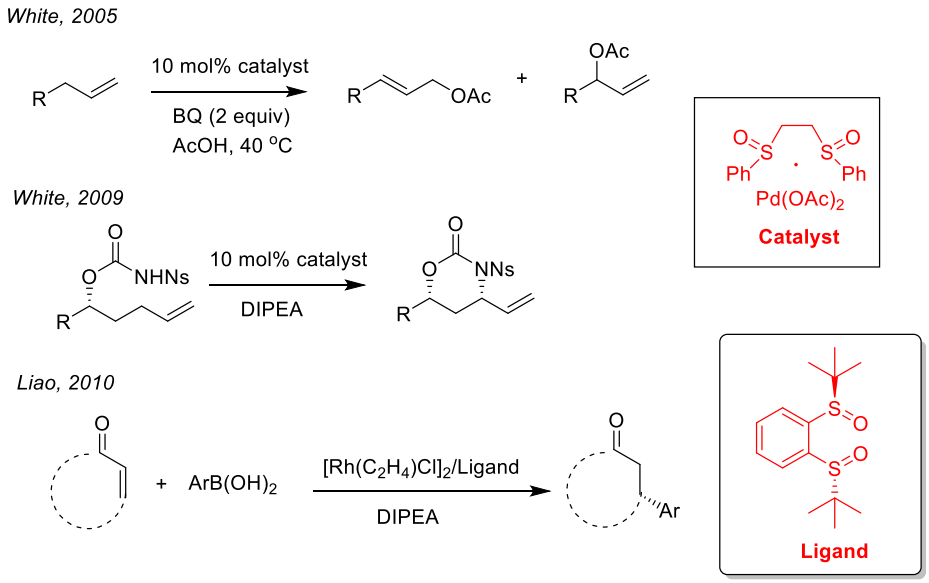
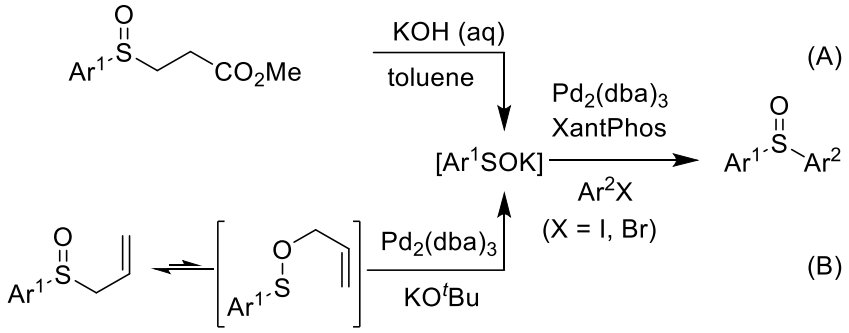


Figure 2-2. Representative sulfoxide ligands in transition metal catalysis

2.1.2 Aryl Sulfoxide Generation via Palladium Catalyzed *S*-Arylation of Sulfenate anions.

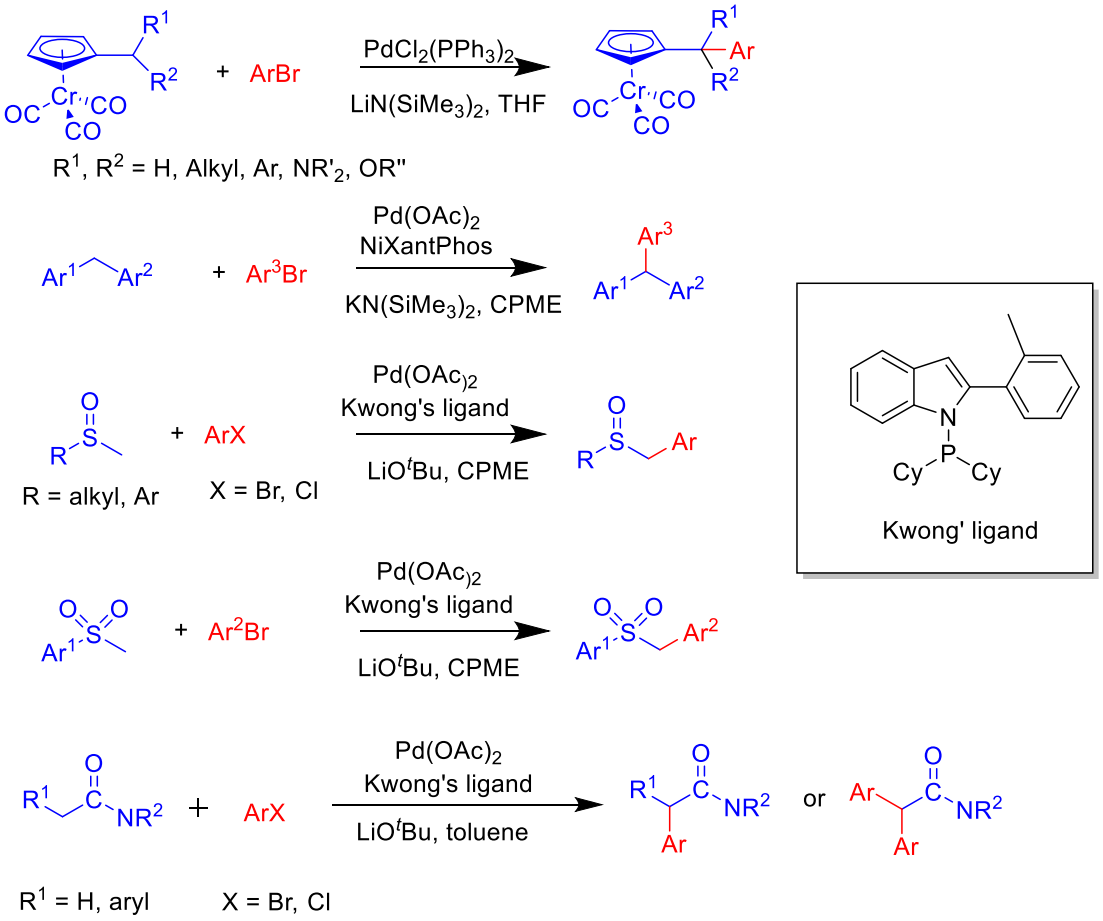
In 2006, Madec and Poli reported preparation of aryl sulfoxides via Pd-catalyzed arylation of sulfenate anions with aryl iodides and bromides (Scheme 2-1, eq. A&B).[8] In the presence of 20 equiv of KOH, sulfenate anions could be generated from retro-Michael addition of β-sulfinyl esters (Scheme 2-1, eq. A).[8a,b] In a second report, a palladium-catalyzed C–O bond cleavage of allylic sulfenate esters via Mislow-Braverman-Evans rearrangement of the allylic sulfoxides was reported (Scheme 2-1, eq. B).[8c] Subsequently, the sulfenate anions were arylated with aryl iodides or bromides to yield diaryl sulfoxides. The substrate scope of these reactions is narrow.



Scheme 2-1. Synthetic approaches to diaryl sulfoxides via palladium catalyzed *S*-arylation of sulfenate anions

2.1.3 Our Approach to Diaryl Sulfoxides via Palladium Catalyzed Arylation of Sulfenate Anions.

Palladium catalyzed arylation is a powerful tool in organic synthesis.[9] We recently reported the palladium-catalyzed functionalization of weakly acidic sp^3-hybridized C–H bonds (pK_as 28–35 in DMSO) via deprotonative cross-coupling process (DCCP). Using this approach, we developed coupling protocols for diarylmethanes,[10] sulfoxides,[11] sulfones,[12] amides,[13] and chromium-activated benzylic amines (to produce enantioenriched diarylmethylamines).[14] During our study on the α-arylation of sulfoxides using Kwong's ligand,[15] we noticed that a diaryl sulfoxide byproduct was generated in up to 20% yield from benzyl phenyl sulfoxide with 4-*tert*-butyl bromobenzene. Therefore, we envisioned a novel protocol to produce diaryl sulfoxides from aryl benzyl sulfoxides and aryl bromides.



Scheme 2-2. Palladium catalyzed arylation of diarylmethanes, sulfoxides, sulfones, amides, and chromium-activated benzylic amines via DCCP

2.2 Results and Discussion

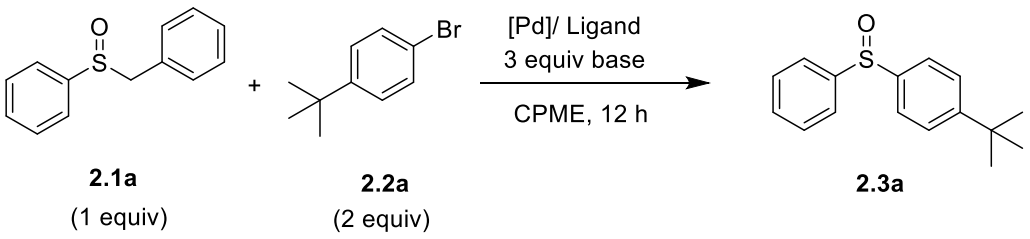
2.2.1 Optimization of Palladium Catalyzed Diaryl Sulfoxide Formation

During our study on the alpha arylation of sulfoxides using Kwong's indole-based ligand **2.L1**,[15] we noticed that a diaryl sulfoxide byproduct (**2.3a**) was generated in up to 20% yield from benzyl phenyl sulfoxide (**2.1a**) with 4-*tert*-butyl bromobenzene (**2.2a**) under arylation conditions [10 mol % $Pd(OAc)_2$, 15 mol % **2.L1**, 3 equiv LiO^tBu, in cyclopentyl methyl ether (CPME) at 110 ^oC for 12 h, Table 2-1, entry 1].

We initiated the optimization by performing a ligand screen using the conditions described in Table 2-1. Of the 112 sterically and electronically diverse mono- and bidentate phosphine ligands examined, two classic Buchwald ligands [SPhos (**2.L2**) and DavePhos (**2.L3**)] along with van Leeuwen's NiXantPhos (**2.L4**)[16] outperformed Kwong's indole-based phosphine (**2.L1**, Table 2-1). On a laboratory scale, the yields of **2.3a** with SPhos, DavePhos, and NiXantPhos were 25%, 33%, and 22%, respectively (Table 2-1, entry 1 *vs* entries 2–4). Because the role of the base is crucial to DCCP reactions, we next examined twelve bases and four solvents using ligands SPhos (**2.L2**) DavePhos (**2.L3**), and NiXantPhos (**2.L4**) (See Experimental Section for details). The highest yield was with 15 mol % NiXantPhos **2.** (**L4**) and 10 mol % $Pd(OAc)_2$ in the presence of NaO^tBu in CPME, generating **2.3a** in 83% yield (Table 2-1, entry 5). Forging ahead with NiXantPhos, a similar yield was obtained when the temperature was reduced to 80 ^oC (entry 6). Examination of four palladium sources [$Pd(OAc)_2$, $Pd(COD)Cl_2$, $Pd(NCCH_3)_2Cl_2$ and $Pd_2(dba)_3$] in six solvents was undertaken using NiXantPhos (**2.L4**) as ligand and NaO^tBu as base at 80 ^oC for 12 h. Among the variables examined, $Pd_2(dba)_3$ in CPME rendered the highest assay yield on microscale High-Throughput Experimentation (HTE). Unfortunately, we were unable to translate these conditions to laboratory scale, and only 55% yield of **3a** was obtained. We hypothesized that contamination of commercial $Pd_2(dba)_3$ with nanoparticles was a potential problem (Table 2-1, entry 7).[17] Changing to $Pd(dba)_2$ overcame this issue, generating **2.3a** in 91% yield (Table 2-1, entry 8). We were able to decrease the Pd/ligand loading from 10/15 mol % to 5/7.5 mol % while maintaining

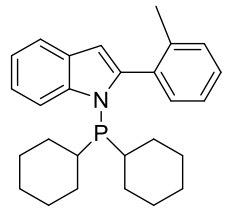
the yield (Table 2-1, entry 9). Reduction to 2.5/3.8 mol % resulted in lower yield (68%, entry 10). Therefore, 5 mol % $Pd(dba)_2$ and 7.5 mol % NiXantPhos were employed. Decreasing the temperature to 55 ^oC was unsuccessful, leading to only 28% yield of **2.3a** (entry 11). Further optimization of the loading of NaO^tBu and the ratios of **2.1a** and **2.2a** revealed that 3 equiv of NaO*t*Bu and a 1:2 ratio of **2.1a**/**2.2a** was optimal. Thus, our best conditions to provide **2.3a** were 5 mol % $Pd(dba)_2$ and 7.5 mol % NiXantPhos (**2.L4**), sulfoxide **2.1a** as the limiting reagent, 2 equiv of aryl bromide **2.2a**, and 3 equiv NaO^tBu as base in CPME at 80 ^oC for 12 h.

Table 2-1. Optimization of diaryl sulfoxide formation by cross-coupling of benzyl phenyl sulfoxide (**2.1a**) with 4-*tert*-butyl bromobenzene (**2.2a**).

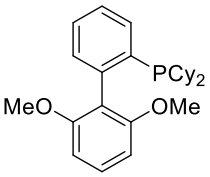


2.1a (1 equiv) **2.2a** (2 equiv) **2.3a**

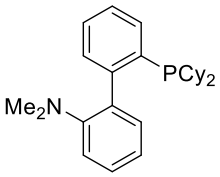
Entry	Catalyst	Ligand	Catalyst/ligand /mol %	Temp. /^oC	Base	Isolated Yield /%
1	$Pd(OAc)_2$	Kwong's ligand (**2.L1**)	10/15	110	LiO^tBu	20
2	$Pd(OAc)_2$	SPhos(**2.L2**)	10/15	110	LiO^tBu	25
3	$Pd(OAc)_2$	DavePhos(**2.L3**)	10/15	110	LiO^tBu	33
4	$Pd(OAc)_2$	NiXantPhos(**2.L4**)	10/15	110	LiO^tBu	22
5	$Pd(OAc)_2$	NiXantPhos(**2.L4**)	10/15	110	NaO^tBu	83
6	$Pd(OAc)_2$	NiXantPhos(**2.L4**)	10/15	80	NaO^tBu	85
7	$Pd_2(dba)_3$	NiXantPhos(**2.L4**)	10/15	80	NaO^tBu	55
8	$Pd(dba)_2$	NiXantPhos(**2.L4**)	10/15	80	NaO^tBu	91
9	$Pd(dba)_2$	NiXantPhos(**2.L4**)	5/7.5	80	NaO^tBu	91
10	$Pd(dba)_2$	NiXantPhos(**2.L4**)	2.5/3.8	80	NaO^tBu	68
11	$Pd(dba)_2$	NiXantPhos(**2.L4**)	5/7.5	55	NaO^tBu	28



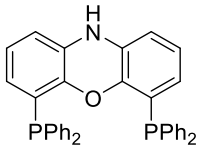
Kwong's ligand (**2.L1**)



SPhos (**2.L2**)



DavePhos (**2.L3**)



NiXantPhos (**2.L4**)

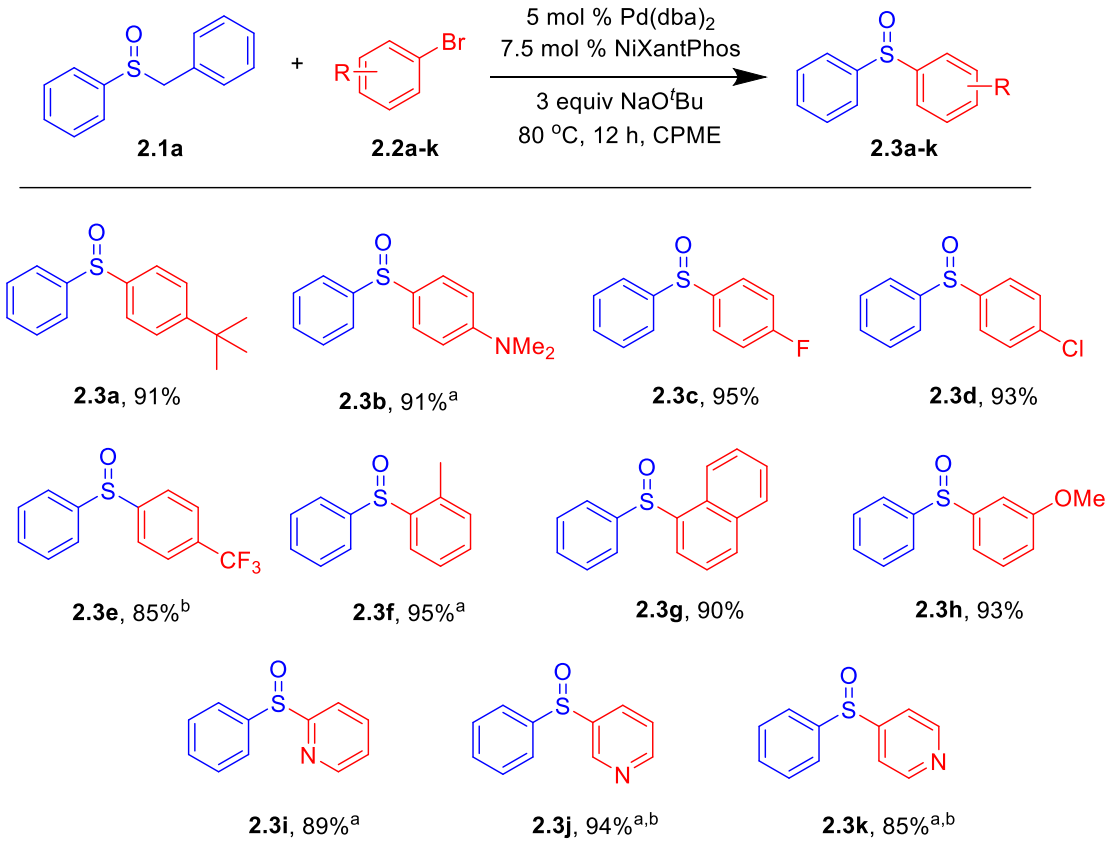
2.2.2 Substrate scope of aryl bromides in palladium catalyzed diaryl sulfoxides formation

The reaction conditions identified for the formation of **2.3a** were evaluated for a series of aryl bromides with sulfoxide **2.1a** (Scheme 2-3). Electron-donating groups on the aryl bromides, such as 4-*tert*-butyl and 4-*N*,*N*-dimethylamino, were well tolerated, providing **2.3a** and **2.3b** both in 91% yield. The cross-coupling reactions proceeded smoothly with **2.1a** and various aryl bromides bearing electron-withdrawing groups, including 4-fluoro (**2.2c**), 4-chloro (**2.2d**), 4-trifluoromethyl (**2.2e**) and 4-nitro (**2.2f**) providing **2.3c**–**f** in 85–95% yield. Excellent chemoselectivity in coupling at bromide over the chloride was achieved with 4-chloro bromobenzene (**2.2d**). The sterically more demanding 2-bromotoluene (**2.2g**) and 1-bromonaphthalene (**2.2h**) furnished products **2.3g** and **2.3h** in 90% and 93% yield, respectively. 3-Bromoanisole generated the coupling product **2.3i** in 93% yield.

Bioactive sulfoxides often contain heterocycles.[18] Our protocol is effective for the synthesis of heterocyclic sulfoxides, as demonstrated with couplings to yield 2-, 3- and 4-pyridyl phenyl sulfoxides (**2.3j**–**l**) in 89, 94 and 85% yields respectively. To

achieve these yields, higher reaction temperatures (110 °C) and longer reaction times (24 h) were needed. It is noteworthy that **2.3j** is the key motif for an anti-inflammatory agent[18a] and **2.3l** is derived from a hair papilla cell proliferation agent.[18b] To show the scalability of our method, we performed the reaction on 5 mmol of benzyl phenyl sulfoxide (**2.1a)** and 10 mmol of 3-bromopyridine (**2.2k**). The product, **2.3k**, was isolated in 86% yield.

Scheme 2-3. Substrate scope of aryl bromides in Pd-catalyzed formation of diaryl sulfoxides with benzyl phenyl sulfoxide (**2.1a**).

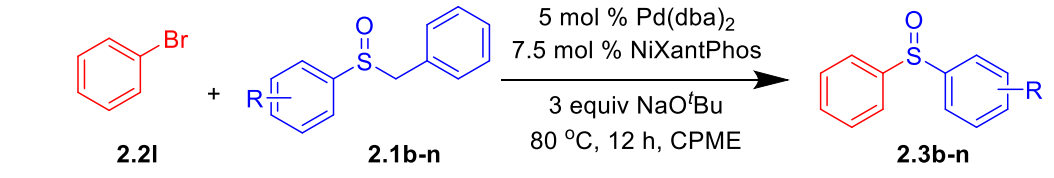


[a] 110 °C; [b] 24 h.

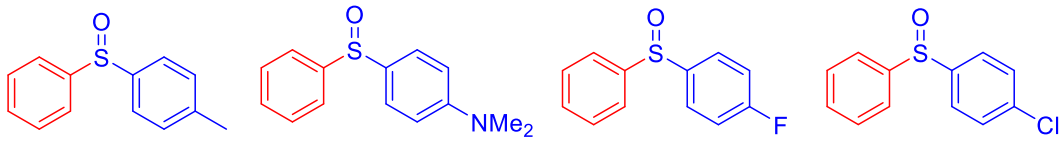
2.2.3 Substrate scope of aryl benzyl sulfoxides in palladium catalyzed diaryl sulfoxides formation

We next turned our attention to the substrate scope of aryl benzyl sulfoxides in coupling reactions with bromobenzene (**2.2m**) to generate diaryl sulfoxides. Electron-donating 4-methyl and 4-*N*,*N*-dimethylamino groups were well tolerated, giving **2.3m** and **2.3b** in 99 and 92% yield, respectively. Substrates bearing electron-withdrawing 4-F (**2.1c**), 4-Cl (**2.1d**), 4-CF_3 (**2.1e**) groups furnished the products in 86–92% yield. The congested 2-tolyl and 1-naphthyl benzyl sulfoxides **2.1g** and **2.1h** afforded **2.3g** and **2.3h** in 93% and 91% yield, respectively. Aryl heteroaryl sulfoxides were provided from heteroaryl benzyl sulfoxides in excellent yields under slightly modified conditions (see Scheme 2-4 for details). 3-Pyridyl (**2.3k**), 2-furanyl (**2.3n**) and 2-thienyl (**2.3m**) phenyl sulfoxides were thus prepared. Compound **2.3n** could be utilized as a key motif for an antituberculotic reagent.[18c] Alkyl aryl sulfoxides could also be prepared, as demonstrated by generation of cyclohexyl phenyl sulfoxide (**2.3p**) in 90% yield.

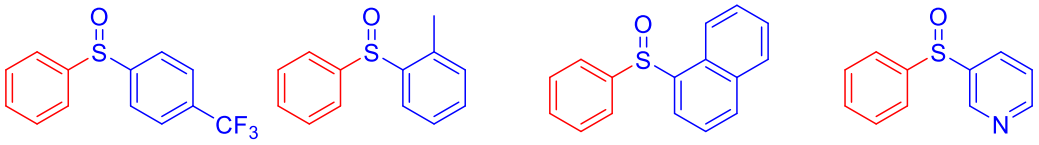
Scheme 2-4. Substrate scope of aryl benzyl sulfoxides in Pd-catalyzed formation of diaryl sulfoxides with bromobenzene (**2.2m**).



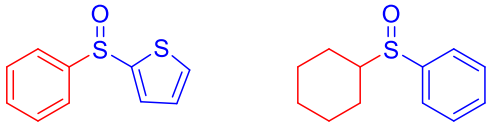
2.2l **2.1b-n** **2.3b-n**



2.3l, 99% **2.3b**, 92% **2.3c**, 92% **2.3d**, 91%[a]



2.3e, 86% **2.3f**, 93%[b] **2.3g**, 91% **2.3j**, 89%[a]



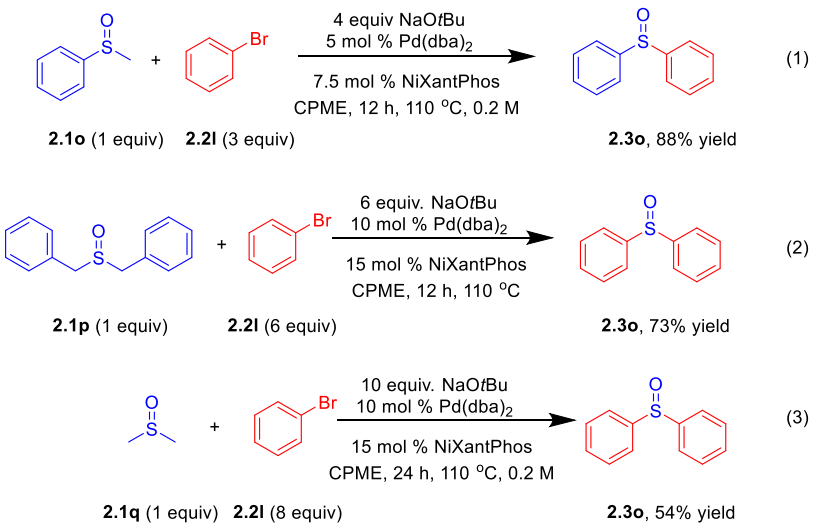
2.3m, 85%[b] **2.3n**, 90%[b]

[a] 24 h; [b] 110 °C.

2.2.4 Palladium catalyzed tandem diaryl sulfoxide formation

We recently reported the first palladium-catalyzed alpha arylation of methyl sulfoxides with aryl halides.[11] The products generated from this alpha arylation approach were aryl benzyl sulfoxides, which were employed as the starting materials in this work. Thus, we were interested in exploring the synthesis of diaryl sulfoxides directly from aryl methyl sulfoxides. The challenge to combine the previous α-arylation procedure and the current cross-coupling reaction was to identify a single catalyst and conditions that efficiently promote the different reactions. Fortunately, the $Pd(dba)_2$/NiXantPhos system proved to be suitable for this transformation (Scheme 2-5, eq. 1). Thus, starting with methyl phenyl sulfoxide (**2.1o**) diphenyl

sulfoxide (**2.3o**) was generated directly in 88% yield using 0.2 M concentration. This tandem synthetic route broadens the substrate scope and makes the process more efficient by reducing the number of isolations and purifications. Encouraged by this interesting one-pot protocol to form diphenyl sulfoxide from **2.1o**, we sought to generate diphenyl sulfoxide starting from dibenzyl sulfoxide (**2.1p**) via dual palladium-catalyzed cross-coupling reactions (Scheme 2-5, eq. 2). The desired product **2.3o** was provided in 73% yield from **2.1p** upon increasing the catalyst/ligand loading to 10/15 mol %. Interestingly, dimethyl sulfoxide (DMSO), a commonly used solvent, could also be utilized as suitable reactant in our approach. DMSO underwent dual alpha arylation/cross-coupling to generate diaryl sulfoxide **2.3o** in 54% yield (Scheme 2-5, eq. 3).



Scheme 2-5. Tandem Pd-catalyzed synthesis of diphenyl sulfoxide (**2.3o**) from methyl phenyl sulfoxide (**2.1o**), benzyl sulfoxide (**2.1p**) and dimethyl sulfoxide (DMSO) (**2.1q**).

2.2.5 Mechanism study of palladium catalyzed diaryl sulfoxide formation from

aryl benzyl sulfoxides and aryl bromides

To generate diaryl sulfoxides, the Pd/NiXantPhos catalyst must promote multiple distinct reactions, including cleavage and formation of C–S bonds. Based on experiments discussed below, a tricatalytic cycle is proposed in Figure 2-3. The first cycle (**A**), is the alpha arylation of aryl benzyl sulfoxides. We recently reported a similar catalytic arylation of methyl phenyl sulfoxides in up to 95% yield and one example of arylation of a benzyl phenyl sulfoxide (80% yield).[11] Support for cycle **A** was gained when the temperature was decreased from 110 ^{o}C to 80 ^{o}C (Scheme 2-6A) in the reaction of benzyl phenyl sulfoxide (**2.1a**) with 2-tolyl bromide (**2.2g**). We isolated the diarylmethyl sulfoxide, **2.4g** (intermediate **V**, Figure 2-3), in 5% yield along with 35% diaryl sulfoxide **2.3g** (Scheme 2-6A). These results support the proposed α-arylation cycle **A**. Subsequently, diphenylmethyl phenyl sulfoxide (**2.4a**) was synthesized independently and subjected to the optimized reaction conditions with 4-*tert*-butyl bromobenzene. The diaryl sulfoxide product **2.3a** was generated in 88% yield (Scheme 2-6B).

In the second catalytic cycle (**B**) a novel cleavage of the C–S bond occurs. Arene coordination of the aryl diarylmethyl sulfoxide moiety (**VI**) to Pd is followed by formation of a π-benzyl intermediate (**VII**) and expulsion of aryl sulfenate (**VIII**, Figure 2-3). The π-benzyl intermediate (**VII**) is attacked by the NaO^{t}Bu base, generating diarylmethyl *tert*-butyl ether (**X**), which we have isolated from the reaction mixture. The yield of this byproduct is always significantly lower than expected based on the reaction stoichiometry. Further studies demonstrated that the $Ar_2CH–O–^{t}Bu$

undergoes a base induced E2-elimination to generate $Ar_2CH–ONa$, which is oxidized by palladium in a fourth catalytic cycle. When 3 equiv of 4-nitro bromobenzene are employed, nitrobenzene is isolated in 76% yield. If 2 equiv of aryl bromide is used, we propose the eliminated isobutylene is reduced to isobutane.

Palladium π-benzyl intermediates were pioneered by Fiaud and Kuwano,[19] who have developed them into useful synthetic intermediates. We are not aware, however, of previous observation of sulfenates as leaving groups in π-benzylation reactions.

The sulfenate generated in cycle **B** undergoes palladium catalyzed cross-coupling with aryl bromides in cycle **C** and produces the diaryl sulfoxide.

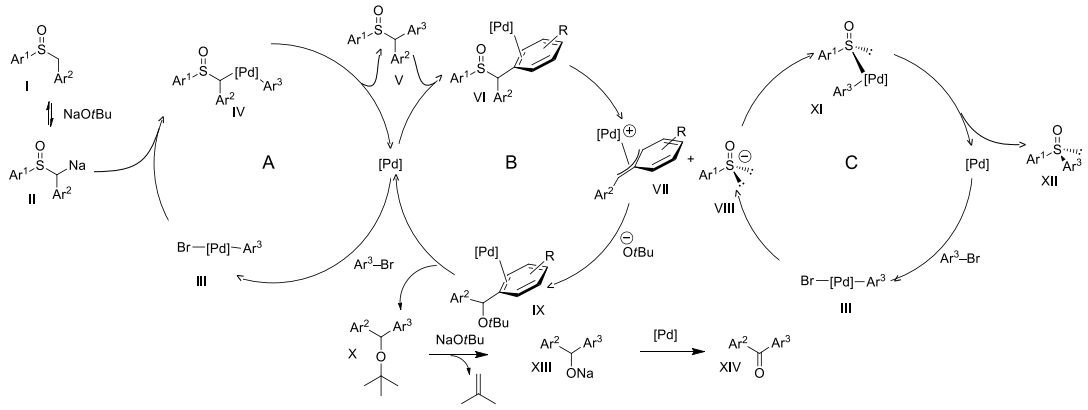
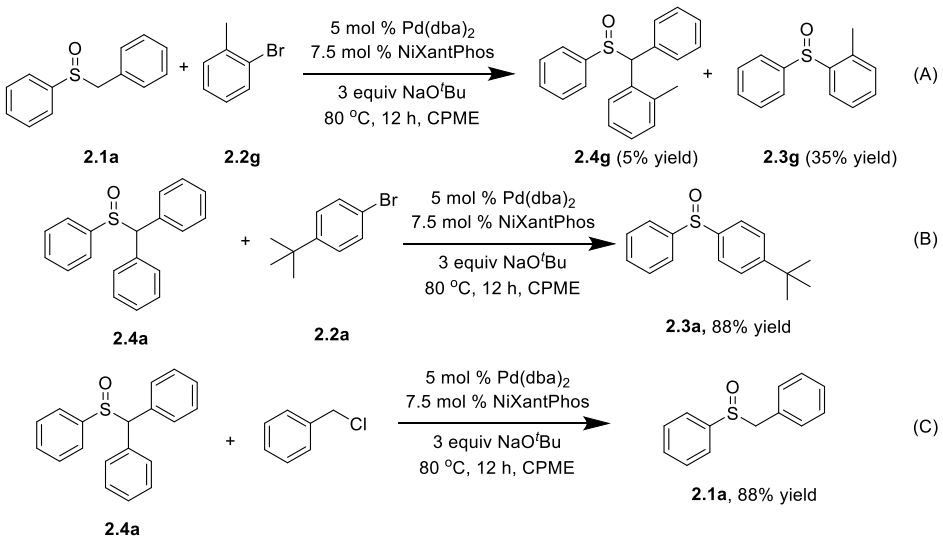


Figure 2-3. Proposed mechanism of the palladium-catalyzed triple relay process.



Scheme 2-6. Generation of **2.4g** and alpha arylation and benzylation of **2.4a**.

2.2.6 Mechanism study of generation of diaryl ketones from *tert*-butyl diarylmethyl ether

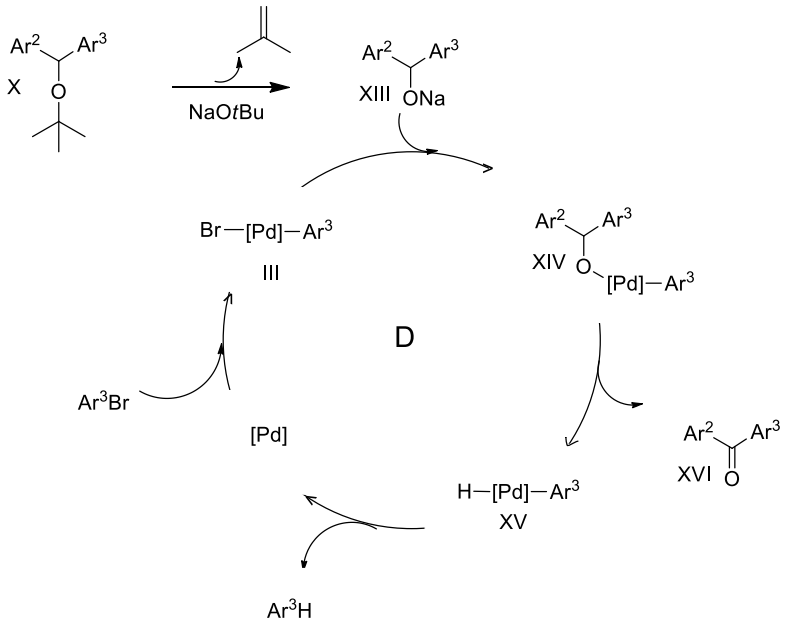


Figure 2-4. Diaryl ketone generation utilizing aryl bromides as oxidizing reagent.

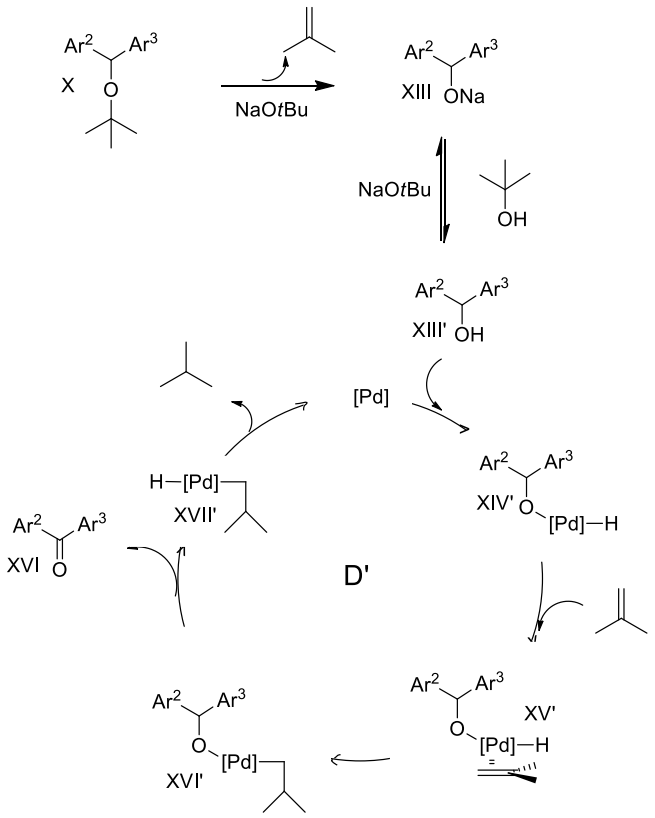
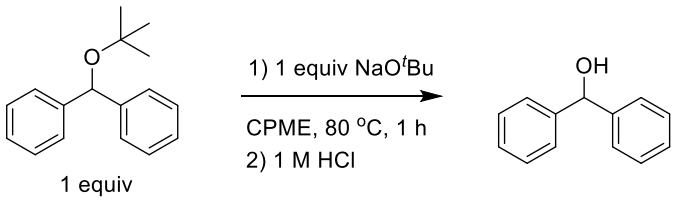


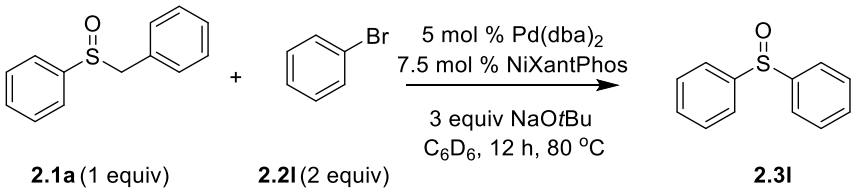
Figure 2-5. Diaryl ketone generation utilizing 2-methylpropene as oxidizing reagent.

To explore the proposed mechanism, the following experiments were performed. When we used 3 equiv of 4-nitro bromobenzene as a cross-coupling partner, nitrobenzene was isolated in 76% yield. The diaryl sulfoxide **2.3f** was isolated in 95% yield. If we used 2 equiv of 4-nitro bromobenzene (**2.2f**), we have isolated the sulfoxide (**2.3f**) in 94% yield, and only 5% of nitrobenzene was isolated. These tests demonstrated that aryl bromide was the reducing agent (see Figure 2-4). Similar oxidation pathways have been previously reported by the Uemura and Stahl groups.[20] We found that diaryl ketone could not be generated completely from catalytic cycle D, since only 2 equiv of aryl bromides were used in the cross coupling reactions. Therefore, diaryl methyl *tert* butyl ether (X, Figure 2-4) could be isolated or observed in some cases.



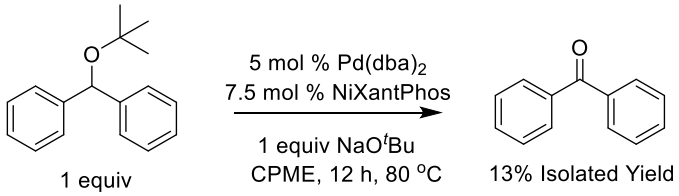
Scheme 2-7. Generation of diphenyl methanol from diphenyl methyl *tert* butyl ether.

Next, we tested the E2 elimination of the *tert* butyl ether to provide the corresponding diaryl methanol (Scheme 2-7). As shown in Scheme 2-7, the E2 elimination process generates diphenyl methanol. To confirm the formation of 2-methylpropene in our reaction, the coupling reaction was performed in C_6D_6 in a sealed J. Young NMR tube, and we observed the formation of 2-methylpropene by ^{1}H NMR. 2-methylpropene is a potential hydrogen acceptor in the catalytic reaction that generated benzophenones. Unfortunately, we could not observe 2-methylpropene generation because its signals overlap with the large *tert*-butanol resonance. Based on these experimental results, we proposed the plausible catalytic cycle D' (see Scheme 2-8 for details).



Scheme 2-8. Monitoring formation of 2-methylpropene in J. Young NMR tube by ^{1}H NMR.

An experiment to test the possibility of generating benzophenone directly from *tert* butyl diphenyl methyl ether catalyzed by Pd(dba)$_2$/NiXantPhos without adding aryl bromide was performed (Scheme 2-9). Although only 13% of benzophenone was isolated, because the reaction was not optimized, this result does suggest that benzophenone can be formed from Pd(0). Such a "palladium-catalyzed hydrogen transfer" (Figure 2-5) mechanism was pioneered by Hayashi.[21]



Scheme 2-9. Monitoring formation of benzophenone without aryl bromide.

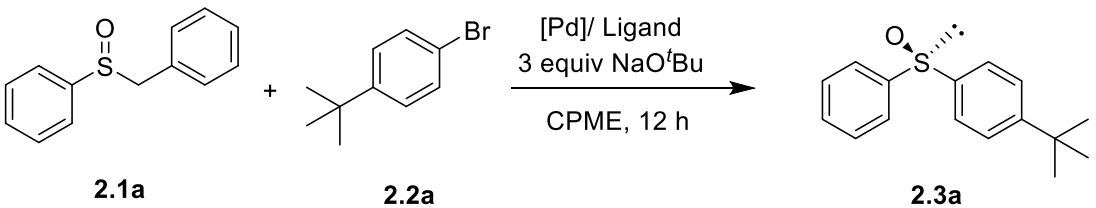
2.2.7 Palladium Catalyzed Enantioselective Diaryl Sulfoxides Formation via Triple Relay Process

Our group has developed the palladium-catalyzed alpha arylation of sulfoxides and sulfones via a deprotonative cross-coupling procedure (DCCP). Moreover, we introduced a novel single palladium-catalyzed triple relay mechanism to produce racemic diaryl sulfoxides directly from aryl benzyl sulfoxides and aryl bromides. Considering the key role of sulfenate anion in our triple relay mechanism, we envisioned the possibility to access chiral diaryl sulfoxides.

We decided to set up a model reaction employing benzyl phenyl sulfoxide (**2.1a)** and 4-*tert*-butyl bromobenzene (**2.2a**) for optimization. The optimization process for palladium catalyzed enantioselective diaryl sulfoxide generation was initiated by screening chiral ligands under otherwise identical conditions as our previous racemic protocol (5 mol % $Pd(dba)_2$ as catalyst, 3 equiv NaO^tBu as base, 1 equiv **2.1a** as limiting reagent, 2 equiv **2.2a**, in CPME, 80 ^oC, 12 h) by High-Throughput Experimentation (HTE). Of 252 electronically and sterically diversified mono- or bidentate chiral ligands tested, JosiPhos family ligands outperformed all others in terms of yield and enantiomeric excess (ee). Among them, SL-J002-1 (**2.L5**), SL-J011-1 (**2.L6**), SL-J014-1 (**2.L7**) and SL-J013-1 (**2.L8**) gave the best results on

HTE scale. When we translated this result to laboratory scale, excellent yields of **2.3a** in moderate ee were observed (Table 2-2, entries 1-4). Since ligand **2.L6** is not commercially available, we decided to forge ahead only with the rest of the ligands. Fortunately, the enantiomeric excess of **2.3a** was increased to 93% when the reaction temperature dropped to 50 ^{o}C using **2.L5** as ligand, although the yield of **2.3a** was slightly decreased to 85% (Table 2-2, entry 5). The other two ligands (**2.L7** and **2.L4**) generated **3a** in lower enantiomeric excess (Table 2-2, compare entry 5 vs entries 6, 7). Thus, **2.L5** was determined to be the optimal ligand. The yield of **2.3a** was increased to 95% when 3 equiv **2.2a** was employed as electrophile as well as the reaction time doubled to 24 h (Table 2-2, entry 8). Decreasing the reaction temperature from 50 ^{o}C to 40 ^{o}C has a detrimental effect on the yield of **2.3a**, which dramatically dropped to 23% with similar ee observed (Table 2-2, entry 9). The attempt to decrease the catalyst/ligand loading failed as well, and only 57% yield of **2.3a** was obtained when 2.5/3.8 mol % of $Pd(dba)_2$/**2.L5** was employed. Other parameters, including palladium sources, bases, solvents, and stoichiometry were also investigated, but no better yields were obtained. Therefore, the optimal reaction conditions for palladium catalyzed enantioselective diaryl sulfoxides generation is 5/7.5 mol % $Pd(dba)_2$/**2.L5** as catalyst system, 3 equiv NaO^tBu as base, 1 equiv **2.1a** as limiting reagent, 3 equiv of **2.2a** as electrophile, in CPME at 50 ^{o}C for 24 h, and the desired product **2.3a** was generated in 95% yield and 91% ee.

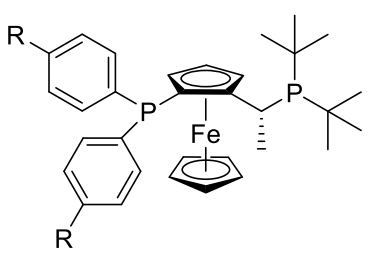
Table 2-2. Optimization of palladium catalyzed enantioselective diaryl sulfoxide generation.



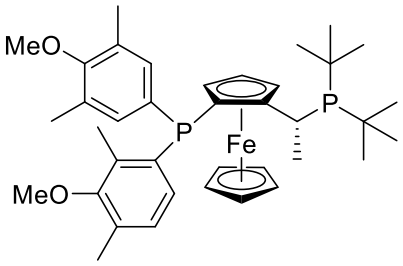
2.1a (1 equiv) + **2.2a** (2 equiv) → **2.3a**

Entry	Catalyst	Ligand	Catalyst/ligand /mol %	Temp. /°C	Isolated Yield (ee) /%
1	$Pd(dba)_2$	SL-J002-1(**2.L5**)	5/7.5	80	95 (75)
2	$Pd(dba)_2$	SL-J011-1(**2.L6**)	5/7.5	80	96 (71)
3	$Pd(dba)_2$	SL-J014-1(**2.L7**)	5/7.5	80	94 (73)
4	$Pd(dba)_2$	SL-J013-1(**2.L8**)	5/7.5	80	94 (70)
5	$Pd(dba)_2$	SL-J002-1(**2.L5**)	5/7.5	50	85 (93)
6	$Pd(dba)_2$	SL-J014-1(**2.L7**)	5/7.5	50	87 (82)
7	$Pd(dba)_2$	SL-J013-1(**2.L8**)	5/7.5	50	64 (80)
8[a]	$Pd(dba)_2$	SL-J002-1(**2.L5**)	5/7.5	50	95 (91)
9[a]	$Pd(dba)_2$	SL-J002-1(**2.L5**)	5/7.5	40	23 (91)
10[a]	$Pd(dba)_2$	SL-J002-1(**2.L5**)	2.5/3.8	50	57 (91)

[a] 3 equiv **2a** used, 24 h.



R = H, SL-J002-1 (**2.L5**)
R = CF_3, SL-J011-1 (**2.L6**)
R = F, SL-J014-1 (**2.L7**)



SL-J013-1 (**2.L8**)

2.3 Conclusion

In summary, we report a novel triple relay process to generate diaryl sulfoxides directly from aryl benzyl sulfoxides and aryl bromides. $Pd(dba)_2$/NiXantPhos efficiently catalyzed the reactions, and a variety of diaryl sulfoxides, as well as alkyl

aryl sulfoxides, were produced in good to excellent yields. Mechanistic studies indicate three distinct core catalytic cycles: sulfoxide α-arylation, C–S bond cleavage and C–S bond-formation. Byproduct benzophenone is formed by an additional palladium-catalyzed process. The palladium catalyzed benzylative C–S bond cleavage of sulfoxides is unprecedented. The palladium catalyzed enantioselective diaryl sulfoxides generation was also developed.

2.4 Experimental Section

General Methods: All reactions were carried out under dry nitrogen. Anhydrous cyclopentyl methyl ether **(**CPME), dioxane, dichloroethane, and 2-MeTHF were purchased from Sigma-Aldrich and directly used without further purification. Toluene and THF were dried through activated alumina columns. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Matrix Scientific or Frontier Scientific, and solvents were purchased from Fisher Scientific and Sigma-Aldrich. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with $KMnO_4$. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling

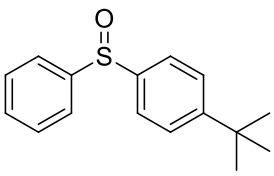
constants are reported in Hertz. The infrared spectra were taken with KBr plates with a Perkin-Elmer Spectrum 1600 Series spectrometer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and were uncorrected.

Preparation of sulfoxides: Sulfoxides were prepared according to the literature procedures.[22,23,24]

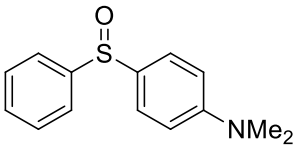
Procedure and Characterization for Formation of Diaryl Sulfoxides by Cross-Coupling Reactions.

General Procedure for catalysis: To an oven-dried microwave vial equipped with a stirbar was added $Pd(dba)_2$ (2.88 mg, 0.005 mmol) and ligand **2.L4** (4.14 mg, 0.0075 mmol) under nitrogen atmosphere followed by 1.0 mL dry CPME. After the catalyst/ligand solution was stirred for 2 h at 24 ℃, NaO^tBu (28.8 mg, 0.30 mmol, 3 equiv) was added to the reaction vial followed by benzyl phenyl sulfoxide (21.6 mg, 0.10 mmol, 1.0 equiv). The microwave vial was sealed, and 4-*tert*-butyl bromobenzene (34.6 μL, 0.20 mmol, 2.0 equiv) was added by syringe under a nitrogen atmosphere. Note that if the benzyl sulfoxide or aryl bromide is a solid, it was added to the reaction vial before NaO^tBu. The reaction mixture was heated to 80 ℃ by oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and the reaction mixture was passed through a short pad of silica gel.

The pad was then rinsed with 10:1 dichloromethane:methanol. The solvent was removed under reduced pressure to yield a white solid. The residue was purified by flash chromatography as outlined below.

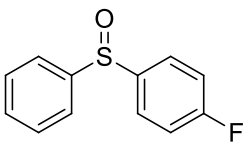


1-(*tert*-Butyl)-4-(phenylsulfinyl)benzene (2.3a): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 4-*tert*-butyl bromobenzene (**2.2a**) (34.6 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (23.5 mg, 91% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1); m.p. = 89 – 91 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.47 – 7.44 (m, 5H), 1.29 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 154.7, 145.6, 142.2, 130.8, 129.2, 126.4, 124.8, 124.7, 34.9, 31.1 ppm; IR (thin film): 2962, 1655, 1443, 1086, 1046, 830, 750, 690 cm^{-1}; HRMS calculated for $C_{16}H_{19}OS$ 259.1157, found 259.1161 $[M+H]^+$.

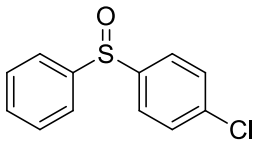


***N*,*N*-Dimethyl-4-(phenylsulfinyl)aniline (2.3b):** The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 4-bromo-*N*,*N*-dimethylaniline (**2.2b**) (40.0 mg, 0.20 mmol) at 110 ℃ for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (22.3 mg, 91% yield) as a white solid. R_f = 0.2 (hexanes:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8 Hz, 2H), 7.45 – 7.37 (m, 5H), 2.96 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ

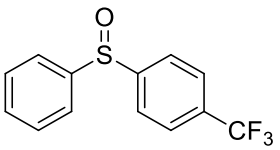
152.4, 146.2, 130.7, 130.1, 128.9, 127.7, 124.5, 111.9, 40.1 ppm; HRMS calculated for $C_{14}H_{16}OSN$ 246.0953, found 246.0955 $[M+H]^+$; m.p. and IR were reported previously.[25]



1-Fluoro-4-(phenylsulfinyl)benzene (2.3c): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 1-bromo-4-fluorobenzene (**2.2c**) (22.0 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (20.9 mg, 95% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]

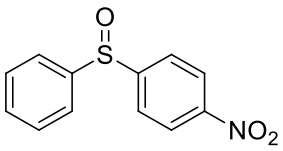


1-Chloro-4-((phenylsulfinyl)methyl)benzene (2.3d): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 1-bromo-4-chlorobenzene (**2.2d**) (23.2 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (22.0 mg, 93% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]

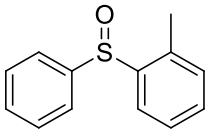


1-(Phenylsulfinyl)-4-(trifluoromethyl)benzene (2.3e): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 4-bromobenzotrifluoride (**2.2e**) (28.0 μL, 0.20 mmol) at 80 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with

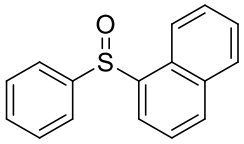
EtOAc:hexanes = 1:4) to give the product (23.0 mg, 85% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 3.5 Hz, 2H),7.46 (d, *J* = 3.5 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 149.9, 144.9, 132.8 (q, *J* = 32.8 Hz), 131.6, 129.6, 126.3 (q, *J* = 3.6 Hz), 124.8, 123.6 (q, *J* = 59.8 Hz) ppm; IR (thin film): 2924, 1605, 1444, 1400, 1323, 1168, 1128, 1058, 1014, 839, 750, 694 cm^{-1}; HRMS calculated for $C_{13}H_{10}OSF_3$ 271.0404, found 271.0405 $[M+H]^+$. m. p. was reported previously.[27]



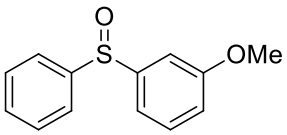
1-Nitro-4-(phenylsulfinyl)benzene (2.3f): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 1-bromo-4-nitrobenzene (**2.2f**) (40.2 mg, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (23.2 mg, 94% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



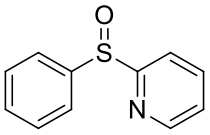
1-Methyl-2-(phenylsulfinyl)benzene (2.3g): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 2-bromotoluene (**2.2g**) (24.1 μL, 0.20 mmol) at 110 ℃ for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (20.5 mg, 95% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



1-(Phenylsulfinyl)naphthalene (2.3h): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 1-bromonaphthalene (**2.2h**) (28.0 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (22.7 mg, 90% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21(m, 2H), 7.93 (d, *J* = 8 Hz, 1H), 7.87 (dd, *J* = 7, 5.5 Hz, 1H), 7.66 (dd, *J* = 2, 8 Hz, 2H), 7.61 (t, *J* = 8 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.38 – 7.33 (m, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 145.1, 140.5, 133.7, 131.0, 129.3, 129.2, 128.9, 127.3, 126.7, 125.5, 125.3, 124.1, 122.5 ppm; IR (thin film): 3055, 2922, 2852, 1725, 1589, 1442, 1260, 1139, 1081, 1045, 801, 770, 748, 688 cm^{-1}; HRMS calculated for $C_{16}H_{13}OS$ 253.0687, found 253.0688 $[M+H]^+$; m. p. was reported previously.[28]

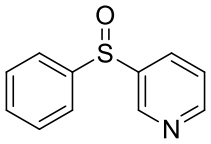


1-Methoxy-3-(phenylsulfinyl)benzene (2.3i): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and 3-bromoanisole (**2.2i**) (25.3 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (21.6 mg, 93% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]

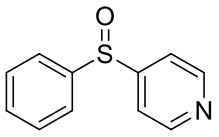


2-(Phenylsulfinyl)pyridine (2.3j): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol),

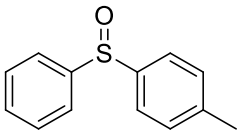
NaO^tBu (28.8 mg, 0.30 mmol) and 2-bromopyridine (**2.2j**) (19.1 μL, 0.20 mmol) at 80 ℃ for 6 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc) to give the product (18.1 mg, 89% yield) as a white solid. R_f = 0.5 (EtOAc:Hexanes= 1:1). The spectroscopic data match the previously reported data.[29]



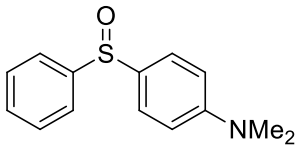
3-(Phenylsulfinyl)pyridine (2.3k): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^tBu (28.8 mg, 0.30 mmol) and 3-bromopyridine (**2.2k**) (19.3 μL, 0.20 mmol) at 110 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc) to give the product (19.1 mg, 94% yield) as a white solid. R_f = 0.4 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (d, *J* = 2 Hz, 1H), 8.63 (dd, *J* = 5, 1.5 Hz, 1H), 7.96 (dt, *J* = 8, 2 Hz, 2H), 7.65 – 7.62 (m, 2H), 7.48 – 7.44 (m, 3H), 7.38 (dd, *J* = 8, 5 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.9, 146.4, 144.5, 142.3, 132.3, 131.6, 129.6, 124.6, 124.2 ppm. Other spectroscopic data match the previously reported data.[26]



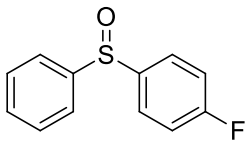
4-(Phenylsulfinyl)pyridine (2.3l): The reaction was performed following the General Procedure with **2.1a** (21.6 mg, 0.10 mmol), NaO^tBu (48.1 mg, 0.50 mmol) and 4-bromopyridine hydrochloride (**2.2l**) (38.9 mg, 0.20 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc) to give the product (17.3 mg, 85% yield) as a white solid. R_f = 0.4 (EtOAc). The spectroscopic data match the previously reported data.[29]



1-Methyl-4-(phenylsulfinyl)benzene (2.3m): The reaction was performed following the General Procedure with 1-(benzylsulfinyl)-4-methylbenzene (23.0 mg, 0.10 mmol) (**2.1m**), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (21.4 mg, 99% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc). The spectroscopic data match the previously reported data.[26]

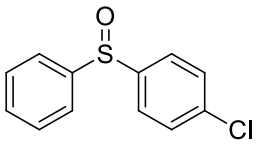


***N,N*-Dimethyl-4-(phenylsulfinyl)aniline (2.3b) (from 4-(benzylsulfinyl)-*N,N*-dimethylaniline):** The reaction was performed following the General Procedure with 4-(benzylsulfinyl)-*N,N*-dimethylaniline (25.9 mg, 0.10 mmol) (**2.1b**), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (22.5 mg, 92% yield) as a white solid. R_f = 0.2 (hexanes:EtOAc = 2:1).

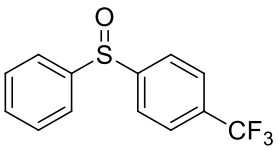


1-Fluoro-4-(phenylsulfinyl)benzene (2.3c) (from 1-(benzylsulfinyl)-4-fluorobenzene): The reaction was performed following the General Procedure with 1-(benzylsulfinyl)-4-fluorobenzene (**2.1c**) (23.4 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4)

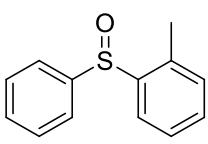
to give the product (20.2 mg, 92% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



1-Chloro-4-((phenylsulfinyl)methyl)benzene (2.3d) (from 1-(benzylsulfinyl)-4-chlorobenzene): The reaction was performed following the General Procedure with 1-(benzylsulfinyl)-4-chlorobenzene (**2.1d**) (25.1 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol) at 80 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (21.7 mg, 91% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]

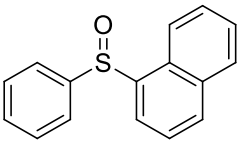


1-(Phenylsulfinyl)-4-(trifluoromethyl)benzene (2.3e) (from 1-(benzylsulfinyl)-4-(trifluoromethyl)benzene): The reaction was performed following the General Procedure with 1-(benzylsulfinyl)-4-(trifluoromethyl)benzene (**2.1e**) (28.4 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (23.2 mg, 86% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1).

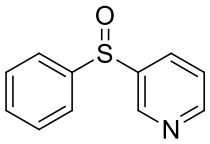


1-Methyl-2-(phenylsulfinyl)benzene (2.3g) (from 1-(benzylsulfinyl)-2-methylbenzene): The reaction was performed following the General Procedure with

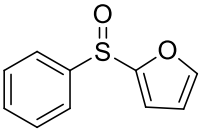
1-(benzylsulfinyl)-2-methylbenzene (**2.1g**) (23.0 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol) at 110 °C for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (20.1 mg, 93% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



1-(Phenylsulfinyl)naphthalene (2.3h) (from 1-(benzylsulfinyl)naphthalene): The reaction was performed following the General Procedure with 1-(benzylsulfinyl)naphthalene (**2.1h**) (26.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (22.9 mg, 91% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1).

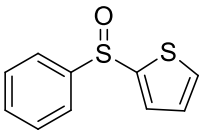


3-(Phenylsulfinyl)pyridine (2.3k) (from 3-(benzylsulfinyl)pyridine): The reaction was performed following the General Procedure with 3-(benzylsulfinyl)pyridine (**2.1k**) (21.7 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol) at 110 °C for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc) to give the product (18.1 mg, 89% yield) as a white solid. R_f = 0.4 (EtOAc).

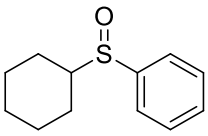


2-(Phenylsulfinyl)furan (2.3n): The reaction was performed following the General Procedure with 2-(benzylsulfinyl)furan (**2.1n)**

(20.6 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (17.3 mg, 90% yield) as a pale yellow oil. R_f = 0.3 (hexanes:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (m, 2H), 7.52 – 7.49 (m, 4H), 6.80 (d, *J* = 3.5 Hz, 1H), 6.43 (dd, *J* = 3.5, 2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.4, 147.3, 141.4, 131.2, 129.2, 124.8, 116.2, 111.2 ppm IR (thin film): 3116, 1476, 1457, 1444, 1129, 1087, 1046, 1008, 750, 689 cm^{-1}.

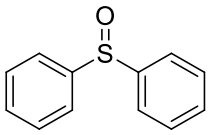


2-(Phenylsulfinyl)thiophene (2.3o): The reaction was performed following the General Procedure with 2-(benzylsulfinyl)thiophene (**2.1o)** (22.2 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol) at 110 °C for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (16.3 mg, 85% yield) as a pale yellow oil. R_f = 0.3 (hexanes:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 2H), 7.58 – 7.55 (m, 2H), 7.51 – 7.24 (m, 3H), 7.05 (dd, *J* = 5, 4 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.8, 145.1, 132.4, 131.4, 131.1, 129.2, 127.2, 124.3 ppm. Other spectroscopic data match the previously reported data.[26]

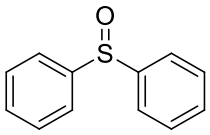


(Cyclohexylsulfinyl)benzene (2.3p): The reaction was performed following the General Procedure with ((cyclohexylsulfinyl)methyl)benzene (**2.1p**) (22.2 mg, 0.10 mmol), NaO^{t}Bu (28.8 mg, 0.30 mmol) and bromobenzene (**2.2m**) (20.9 μL, 0.20 mmol). The crude product was

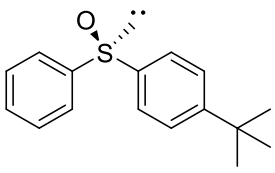
purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:2) to give the product (18.7 mg, 90% yield) as a pale yellow solid. R_f = 0.1 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



Diphenyl sulfoxide (2.3q): The reaction was performed following the General Procedure with $Pd(dba)_2$ (5.76 mg, 0.01 mmol) and ligand **2.L4** (8.28 mg, 0.015 mmol) in 1.0 mL CPME, methyl phenyl sulfoxide (**2.1q**) (28.0 mg, 0.20 mmol), NaO^{t}Bu (57.6 mg, 0.60 mmol) and bromobenzene (**2.2m**) (84.0 μL, 0.80 mmol) at 110 °C for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (35.6 mg, 88% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



Diphenyl sulfoxide (2.3q) (from dibenzyl sulfoxide): The reaction was performed following the General Procedure with $Pd(dba)_2$ (5.76 mg, 0.01 mmol) and ligand **2.L4** (8.28 mg, 0.015 mmol) in 1.0 mL CPME, dibenzyl sulfoxide (**2.1r**) (23.0 mg, 0.10 mmol), NaO^{t}Bu (57.6 mg, 0.60 mmol) and bromobenzene (**2.2m**) (41.8 μL, 0.40 mmol) at 110 °C for 12 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (14.7 mg, 73% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[26]



1-(*tert*-Butyl)-4-(phenylsulfinyl)benzene (3a): The reaction was performed following the General Procedure with

$Pd(dba)_2$ (2.88 mg, 0.005 mmol), SL-J002-1(**2.L5**) (4.1 mg, 0.075 mmol), **2.1a** (21.6 mg, 0.10 mmol), NaO^tBu (28.8 mg, 0.30 mmol) and 4-*tert*-butyl bromobenzene (**2.2a**) (51.9 μL, 0.30 mmol) at 50 ^oC for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (24.5 mg, 91% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1).

High-throughput Experimentation Screenings.

General Experimental for the ligand screening:

Set up:

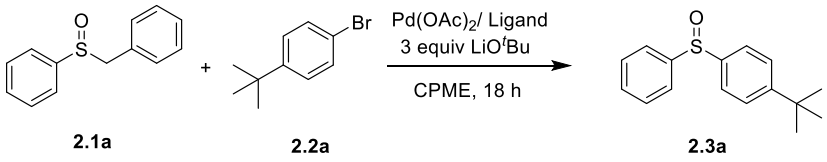
Experiments were set up inside a glovebox under a nitrogen atmosphere. A 96-well aluminum block containing 1 mL glass vials was predosed with $Pd(OAc)_2$ (1 μmol) and the phosphine ligands (2 μmol for monodentate ligands and 1 μmol for bidentate ligands) in THF. The solvent was removed to dryness using a GeneVac and Li*O*t*Bu* (30 μmol) in THF was added to the ligand/catalyst mixture. The solvent was removed on the GeneVac and a stir bar was then added to each reaction vial. Benzyl phenyl sulfoxide (10 μmol/reaction), 4-*tert*-butyl bromobenzene (20 μmol) and biphenyl (1 μmol/reaction) (used as an internal standard to measure HPLC yields) were then dosed together into each reaction vial as a solution in CPME (100 μL, 0.1 M). The 96-well plate was then sealed and stirred for 18 h at 110 °C.

Work up:

Upon opening the plate to air, 500 μL of acetonitrile was added into each vial. The plate was covered again and the vials stirred for 10 min. to ensure good

homogenization. Into a separate 96-well LC block was added 700 μL of acetonitrile, followed by 40 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on an automated HPLC instrument for analysis.

Table 2-3. Ligand screening



Ligands:

	Ligand libraries
1	2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (*t*Bu-XPhos)
2	2-(Dicyclohexylphosphino)-2'-methylbiphenyl (MePhos)
3	2-(Di-*tert*-butylphosphino)-2'-methylbiphenyl (*t*Bu-MePhos)
4	2-(Dicyclohexylphosphino)biphenyl (Cy-JohnPhos)
5	2-Di-*tert*-butylphoshino-2'-(*N*,*N*-dimethylamino)biphenyl (*t*Bu-DavePhos)
6	Racemic-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl
7	1-[2-[Bis(*tert*-butyl)phosphino]phenyl]-3,5-diphenyl-1H-pyrazole (TrippyPhos)
8	5-(Di-*tert*-butylphosphino)-1', 3', 5'-triphenyl-1'H-[1,4']bipyrazole (BippyPhos)
9	Dicyclohexyl-[2-(*o*-tolyl)indol-1-yl]phosphane
10	Di-*tert*-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine (cBRIDP [MoPhos])
11	Dicyclohexyl-(1-methyl-2,2-diphenyl-cyclopropyl)phosphane (Cy-cBRIDP)
12	Dicyclohexyl-(1-methyl-2,2-diphenyl-vinyl)phosphane (Cy-vBRIDP)
13	*N*-phenyl-2-(dicyclohexylphosphino)pyrrole (cataCXium PCy)
14	*N*-phenyl-2-(di-*tert*-butylphosphino)pyrrole (cataCXium PtB)
15	Dicyclohexyl-(1-phenylindol-2-yl)phosphane (cataCXium PInCy)
16	Di-*tert*-butyl-(1-phenylindol-2-yl)phosphane (cataCXium PIntB)
17	1-(2-Methoxylphenyl)-2-(dicyclohexylphosphino)pyrrole (cataCXium POMeCy)
18	Di-*tert*-butyl-[1-(2-methoxyphenyl)pyrrol-2-yl]phosphane (cataCXium POMetB)
19	1-(2,4,6-Trimethylphenyl)-2-(dicyclohexylphosphino)imidazole (cataCXium

	PICy)
20	Di-(2-pyridyl)(dicyclohexylphosphino)amine (cataCXium KCy)
21	Di-(2-pyridyl)(diphenylphosphino)amine (cataCXium KPh)
22	(9-Butylfluoren-9-yl)-dicyclohexyl-phosphonium tetrafluoroborate (cataCXium FBu)
23	Dicyclohexyl-(9-phenethylfluoren-9-yl)phosphonium tetrafluoroborate (cataCXium FPrPh)
24	(9-Benzylfluoren-9-yl)-dicyclohexyl-phosphane; trifluoroborane; hydrofluoride (cataCXium FBn)
25	Trimethylphosphonium tetrafluoroborate
26	Trithylphosphonium tetrafluoroborate
27	Triisopropylphosphonium tetrafluoroborate
28	Tricyclohexylphosphonium tetrafluoroborate
29	Tribenzylphosphine
30	Di-*tert*-butylmethylphosphonium tetrafluoroborate
31	*t*-Butyldicyclohexylphosphine
32	Di-*tert*-butylcyclohexylphosphine
33	Benzyldi-1-adamantylphosphine (cataCXium ABn)
34	Di-*tert*-butylneopentylphosphonium tetrafluoroborate
35	(Z)-1-*tert*-butyl-2,3,6,7-tetrahydro-1H-phosphepinium tetrafluoroborate (Ellman ligand)
36	1,3,5-Triaza-7-phosphaadamantane
37	Di-*tert*-butylphenylphosphonium tetrafluoroborate
38	Dicyclohexylphenylphosphine
39	(*o*-Toyl)dicyclohexylphosphine
40	Dicyclohexyl-(2,4,6-trimethylphenyl)phosphine
41	Dicyclohexyl-(2,6-diisopropylphenyl)phosphine
42	1-Dicyclohexylphosphino-4-dimethylaminobenzene
43	1,3,5,7-Tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphatricyclo[3.3.1.13,7]decane
44	2-(Dicyclohexylphosphino)benzophenone
45	2'-(Dicyclohexylphosphino)acetophenone ethylene ketal
46	1-Di-*iso*-propylphosphino-2-(*N*,*N*-dimethylamino)-1H-indene
47	11-Dicyclohexylphosphino-12-phenyl-9,10-ethenoanthracene (KitPhos)
48	11-Dicyclohexylphosphino-12-(2-methoxyphenyl)-9,10-ethenoanthracene (*o*-Meo-Kitphos)
49	Triphenylphosphine
50	Tri-*o*-tolylphosphine
51	Trimesitylphosphine
52	Tri(2-furyl)phosphine
53	Tris(2-methoxyphenyl)phosphine
54	Tris(4-methoxyphenyl)phosphine
55	Tris(2,4,6-trimethoxyphenyl)phosphine

56	Tris(4-fluorophenyl)phosphine
57	Tris(pentafluorophenyl)phosphine
58	Tris[3,5-bis(trifluoromethyl)phenyl]phosphine
59	Tri(1-naphthyl)phosphine
60	1,2-Bis(diphenylphosphino)ethane monoxide
61	Cyclohexyldiphenylphosphine
62	*tert*-Butyldiphenylphosphine
63	Benzyldiphenylphosphine
64	4-(Dimethylamino)phenyldiphenylphosphine
65	Diphenyl-2-pyridylphosphine
66	2-(1,1-Dimethylpropyl)-6-(diphenylphosphino)pyridine (AlpyPhos)
67	2-(Diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine (ArpyPhos)
68	1-Diphenylphosphino-2-(*N*,*N*-dimethylamino)-1H-indene
69	2-(Diphenylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (Ph-DavePhos)
70	Tris(2,4-di-*tert*-butylphenyl)phosphate
71	(1,1'-Ferrocenediyl)phenylphosphine (1,1'-(PhP)-ferrocene)
72	1,4-Bis(diphenylphosphino)butane monoxide
73	Bis(diphenylphosphino)methane
74	1,2-Bis(diphenylphosphino)ethane (dppe [diphos])
75	1,3-Bis(diphenylphosphino)propane (dppp)
76	1,4-Bis(diphenylphosphino)butane (dppb)
77	1,5-Bis(diphenylphosphino)pentane (dpppe)
78	1,8-Bis(diphenylphosphino)octane (dppo)
79	1,2-Bis(dipentafluorophenylphosphino)ethane
80	1,2-Bis(di-2-pyridylphosphino)ethane
81	1,2-Bis(diphenylphosphinomethyl)benzene
82	1,2-Bis(diphenylphosphino)benzene (dppbz)
83	1,8-Bis(diphenylphosphanyl)naphthalene
84	1,2,3,4-(Diphenylphosphinomethyl)cyclopentane (Tedicyp)
85	Bis(2-diphenylphosphinophenyl)ether (DPEPhos)
86	2,2'-Bis(diphenylphosphino)benzophenone (dpbp)
87	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (XantPhos)
88	4,6-Bis(diphenylphosphino)phenoxazine (NiXantPhos)
89	(*S*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ((*S*)-BINAP)
90	(*R*)-(+)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl ((R)-Tol-BINAP)
91	2,2'-Bis(diphenylphosphino)-1,1'-biphenyl (Biphep)
92	3,3'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro[2,2']binaphthalene hemichloroform adduct (Cy-Nu-Biphep)
93	6,6'-Bis(diphenylphosphino)-1,1',3,3'-tetrahydro[5,5']biisobenzofuran (Thf-Nu-Biphep)
94	Tetramethyl 6,6'-bis(diphenylphosphino)-1,1',3,3'-tetrahydro[5,5']biindenyl-2,2',2,2'-tetracarboxylate

95	2-(Diphenylphosphino)ethylamine
96	2-[2-(Diphenylphosphino)ethyl]pyridine
97	2-Dicyclohexylphosphino-2',4',6'-tri-*iso*-propyl-1,1'-biphenyl (XPhos)
98	2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (SPhos)
99	2-(Di-*tert*-butylphosphino)biphenyl (JohnPhos)
100	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (DavePhos)
101	2-Dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl (RuPhos)
102	2-Di-*t*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (Me-4-*t*Bu-XPhos)
103	Dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (BrettPhos)
104	Butyldi-1-adamantylphosphine (cataCXium A)
105	1,2,3,4,5-Pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (QPhos)
106	Tri-*tert*-butylphosphonium tetrafluoroborate
107	(4-(*N*,*N*-dimethylamino)phenyl)di-*tert*-butyl phosphine (AmPhos)
108	1,1'-Bis(di-*tert*-butylphosphino)ferrocene (dtbpf)
109	1,1'-Bis(diphenylphosphino)ferrocene (dppf)
110	1,1'-Bis(diisopropylphosphino)ferrocene (dippf)
111	(*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ((R)-BINAP)
112	(*R*)-(-)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine (JosiPhos SL-J009-1)

1 – 24: Monodentate dialkyl biaryl phosphine ligands; **25 – 48**: Monodentate trialkyl and dialkylaryl phosphine ligands; **49 – 72**: Monodentate triaryl and diarylalkylphosphine ligands; **73 – 96**: Bidentate electron-poor phosphine ligands; **97 – 108**: Monodentate phosphine ligands; **109 – 112**: Bidentate and Monodentate Phosphine Ligands.

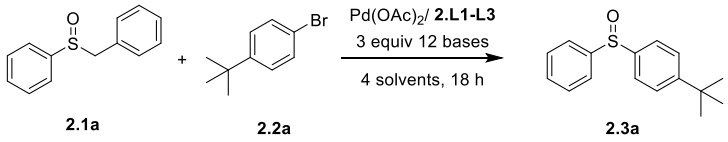
Best results from screening:

Ligand	**Prod/IS**[a]
Kwong's ligand (**2.L1**)	1.23
SPhos (**2.L2**)	4.37

DavePhos (**2.L3**)	2.30
NiXantPhos (**2.L4**)	4.18

[a]Product-internal standard ratio.

Table 2-4. Base and solvent screening

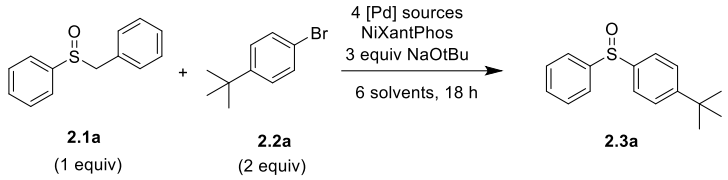


Bases: LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, KN(SiMe$_3$)$_2$, LiH, NaH, LiOAc, CsOAc, KOAc, NaOMe
Solvents: CPME, 1,4-Dioxane, DME, 2-MeTHF

Location	Ligand	Solvent	Base	PROD/IS
A01	SPhos	CPME	LiO*t*Bu	1.21
A02			NaO*t*Bu	2.94
A03			KO*t*Bu	0.00
B01		DIOXANE	LiO*t*Bu	2.24
B02			NaO*t*Bu	2.76
B03			KO*t*Bu	0.40
C01		DME	LiO*t*Bu	2.68
C02			NaO*t*Bu	2.78
C03			KO*t*Bu	0.78
D01		2-MeTHF	LiO*t*Bu	1.77
D02			NaO*t*Bu	2.86
D03			KO*t*Bu	0.30
E01	DavePhos	CPME	LiO*t*Bu	0.99
E02			NaO*t*Bu	3.23
E03			KO*t*Bu	0.00
F01		DIOXANE	LiO*t*Bu	1.76
F02			NaO*t*Bu	1.47
F03			KO*t*Bu	0.30
G01		DME	LiO*t*Bu	2.64
G02			NaO*t*Bu	2.83
G03			KO*t*Bu	0.77
H01		2-MeTHF	LiO*t*Bu	2.09
H02			NaO*t*Bu	2.98
H03			KO*t*Bu	0.19
A01		CPME	LiO*t*Bu	1.47
A02			NaO*t*Bu	4.01

A03	NiXantPhos		KO*t*Bu	1.58
B01		DIOXANE	LiO*t*Bu	2.23
B02			NaO*t*Bu	2.86
B03			KO*t*Bu	0.67
C01		DME	LiO*t*Bu	1.96
C02			NaO*t*Bu	4.07
C03			KO*t*Bu	3.36
D01		2-MeTHF	LiO*t*Bu	2.13
D02			NaO*t*Bu	3.84
D03			KO*t*Bu	2.24

Table 2-5. Pd-source and solvent screening



Location	Catalyst	Solvent	PROD/IS
A01	$Pd(OAc)_2$	CPME	4.01
B01		DIOXANE	2.50
C01		2-MeTHF	3.50
D01		DME	4.34
A02	$Pd(ACN)_2Cl_2$	CPME	5.39
B02		DIOXANE	2.13
C02		2-MeTHF	4.59
D02		DME	5.09
A03	$Pd(TFA)_2$	CPME	5.35
B03		DIOXANE	2.88
C03		2-MeTHF	3.92
D03		DME	5.18
A04	$Pd(COD)Cl_2$	CPME	5.25
B04		DIOXANE	2.23
C04		2-MeTHF	3.89
D04		DME	5.42
A05	Pd_2dba_3	CPME	6.01
B05		DIOXANE	3.47
C05		2-MeTHF	7.28[a]
D05		DME	4.12
A06	$Pd(PPh_3)_4$	CPME	2.63

B06		DIOXANE	4.73
C06		2-MeTHF	3.83
D06		DME	5.28

[a]did not scale well in laboratory

Table 2-6. Ratio **2.2a**:NaO^{t}Bu Screening

Location	**NaO^{t}Bu loading**	**2.2a loading**	**Solvent**	**Prod/IS**
A01	3 equiv	2 equiv	DME	4.12
B01	2 equiv	1.5 equiv	DME	2.12
C01	3 equiv	2 equiv	CPME	6.01
D01	2 equiv	1.5 equiv	CPME	3.52
A02	2 equiv	2 equiv	DME	4.43
B02	4 equiv	1.5 equiv	DME	2.28
C02	1 equiv	2 equiv	CPME	3.01
D02	4 equiv	1.5 equiv	CPME	3.57
A03	2 equiv	2 equiv	DME	3.31
B03	3 equiv	1.2 equiv	DME	1.78
C03	2 equiv	2 equiv	CPME	4.06
D03	3 equiv	1.2 equiv	CPME	3.01
A04	4 equiv	2 equiv	DME	2.43
B04	1 equiv	1.2 equiv	DME	3.14
C04	4 equiv	2 equiv	CPME	4.46
D04	1 equiv	1.2 equiv	CPME	2.92
A05	3 equiv	1.5 equiv	DME	2.11
B05	2 equiv	1.2 equiv	DME	1.99
C05	3 equiv	1.5 equiv	CPME	3.49
D05	2 equiv	1.2 equiv	CPME	3.02
A06	1 equiv	1.5 equiv	DME	3.21
B06	4 equiv	1.2 equiv	DME	1.87
C06	1 equiv	1.5 equiv	CPME	3.17
D06	4 equiv	1.2 equiv	CPME	3.04

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Chapter 3 Palladium-Catalyzed Diaryl Sulfoxides Generation from Aryl Benzyl Sulfoxides and Aryl Chlorides

3.1 Introduction

3.1.1 Introduction to Aryl Sulfoxides

Aryl sulfoxides are important structural motifs in bioactive compounds[1] and marketed therapeutics.[2] They are also widely used as ligands in transition-metal catalysis.[3] Significant effort, therefore, has been devoted to their preparation. The most popular methods for the synthesis of sulfoxides are oxidation of sulfides and nucleophilic substitution of sulfinamides or sulfinate esters.[4]

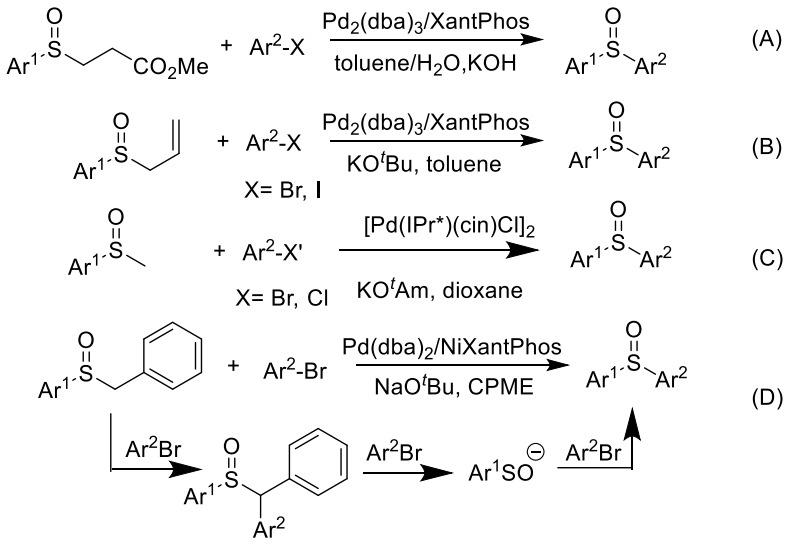
3.1.2 Aryl Sulfoxide Generation via Palladium Catalyzed S-Arylation of Sulfenate Anions

Transition metal catalyzed cross-coupling reactions are powerful methods to form C–S bonds,[5] and offered an alternative approach to construct aryl sulfoxides. In 2007, Poli and Madec reported the first diaryl sulfoxide generation via palladium-catalyzed *S*-arylation between sulfenate anions and aryl bromides and iodides.[6] Sulfenate anions were generated in situ via retro-Michael reaction (Scheme 3-1A). The same team subsequently employed the Mislow-Braverman-Evans rearrangement of allylic sulfoxides and generated sulfenate anions that were arylated in situ to provide diaryl sulfoxides (Scheme 3-1B).[7] Aryl chloride substrates were noticeably absent from these reports.

Very recently, the Nolan group reported an *N*-heterocyclic carbene-based palladium catalyst for the conversion of methyl sulfoxides to diaryl sulfoxides via a proposed

Pd-carbene intermediate (Scheme 3-1C).[8] Although the reaction worked with aryl bromides and chlorides, the only functionalized aryl chloride employed was 4-chloro anisole.

Simultaneously, we communicated diaryl sulfoxide formation from aryl benzyl sulfoxides and aryl bromides using a palladium catalyst based on van Lewueen's NiXantPhos ligand (Scheme 3-1D).[9] A systematic study revealed that this single palladium catalyst promoted three distinct transformations to generate diaryl sulfoxides (Figure 3-1), including α-arylation of benzyl sulfoxides (Cycle A), benzylative substitution of diarylmethyl sulfoxides (Cycle B), and *S*-arylation of sulfenate anions (Cycle C).[10] Various diaryl sulfoxides and heteroaryl aryl sulfoxides were prepared from *aryl bromides* in good to excellent yield.



Scheme 3-1. Aryl sulfoxide syntheses via palladium catalyzed C-S formation

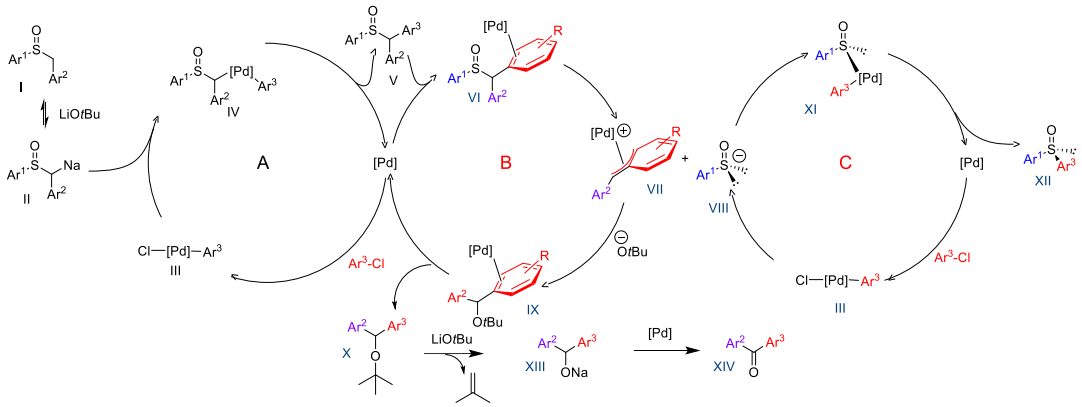
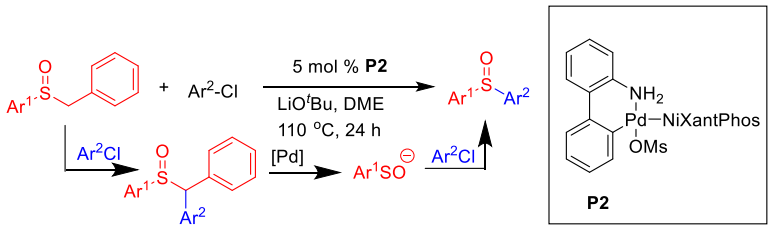


Figure 3-1. Palladium catalyzed diaryl sulfoxides formation from aryl benzyl sulfoxides and aryl chlorides via a triple relay mechanism.

3.1.3 Our Approach to Palladium Catalyzed Diaryl Sulfoxide Generation From Aryl Benzyl Sulfoxides and Aryl Chlorides

Given the scarcity of aryl chlorides that have been successfully employed in the sulfenate anion arylation and the reduced costs and greater abundance of aryl chlorides relative to aryl bromides, we viewed the inclusion of aryl chlorides in this reaction as important.[11] Herein, we report a palladium-catalyzed diaryl sulfoxide formation from aryl benzyl sulfoxides and aryl chlorides (Scheme 3-2).



Scheme 3-2. Palladium catalyzed diaryl sulfoxides generation from aryl benzyl sulfoxides and aryl chlorides

3.2 Results and Discussion

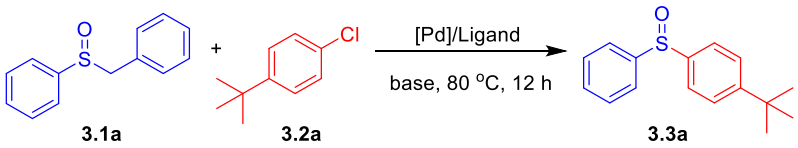
3.2.1 Optimization of Palladium Catalyzed Diaryl Sulfoxide Generation from

Aryl Benzyl Sulfoxides and Aryl Chlorides

We employed coupling partners benzyl phenyl sulfoxide (**3.1a)** and 4-*tert*-butyl chlorobenzene (**3.2a**) as the model substrates to identify reaction conditions. The optimized reaction conditions for coupling sulfoxide **3.1a** with aryl bromides, which involved 5 mol % $Pd(dba)_2$/7.5 mol % NiXantPhos ligand, 3 equiv NaO^tBu base in CPME at 80 ^oC were initially examined (Table 3-1, entry 1).[9] The desired diaryl sulfoxide product (**3.3a**) was formed in less than 5% assay yield. We were concerned that catalyst generation was an issue, so we used Buchwald's palladacyclic precatalysts, which proved to be effective in the oxidative addition of aryl chlorides with NiXantphos.[12] Two palladacyclic precatalysts (**P1** and **P2**, Table 3-1) were prepared according to reported procedures[12f,13] and used under the conditions of the coupling reaction. When **P1** was used with NiXantPhos, the yield of **3.3a** improved to 15%. The yield of **3.3a** increased to 34% when the palladacyclic precursor bearing NiXantPhos (**P2**) was utilized. These low yields inspired us to screen bases that had been successfully applied to other deprotonative cross-coupling processes (DCCP). Thus, LiO^tBu, KO^tBu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$) were investigated. In this screen, LiO^tBu gave the most promising result (43%, Table 3-1, entry 5 vs. entries 4 and 6–9). Three additional ethereal solvents [DME (dimethoxyethane), dioxane and THF] were surveyed, with DME giving the better result yield (51%, Table 3-1, entry 10 vs entries 5, 11 and 12). Increasing the temperature of the reaction from 80 ^oC to 110 ^oC led to 61% yield of **3.3a** (Table 3-1, entry 13). Finally, doubling the reaction time to 24 h resulted in the **3.3a** in 74% assay

yield (^{1}H NMR) and 70% isolated yield (Table 3-1, entry 14). Further optimization did not lead to increased yields. Thus, the optimized conditions for the generation of diaryl sulfoxide **3.3a** from phenyl benzyl sulfoxide (**3.1a**) and 4-*tert*-butyl chlorobenzene (**3.2a**) was 5 mol % palladacyclic precursor **P2**, sulfoxide **3.1a** as the limiting reagent, 2 equiv aryl chloride and, 3 equiv LiO^tBu in DME at 110 ^{o}C for 24 h.

Table 3-1. Optimization of the palladium-catalyzed diaryl sulfoxide formation from benzyl phenyl sulfoxide (**3.1a**) and 4-*tert*-butyl chlorobenzene (**3.2a**).[a]

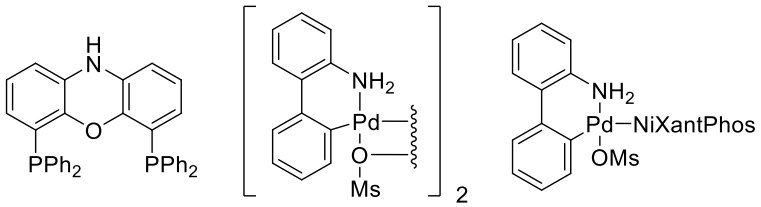


3.1a **3.2a** **3.3a**

entry	Pd/ mol %	base	solvent	assay yield (%)
1[c]	$Pd(dba)_2$/5	NaO^tBu	CPME	<5
2[c]	**P1**/2.5	NaO^tBu	CPME	15
3	**P2**/5	NaO^tBu	CPME	34
4[c]	**P2**/5	NaO^tBu	CPME	29
5	**P2**/5	LiO^tBu	CPME	43
6	**P2**/5	KO^tBu	CPME	27
7	**P2**/5	$LiN(SiMe_3)_2$	CPME	11
8	**P2**/5	$NaN(SiMe_3)_2$	CPME	0

9	**P2**/5	$KN(SiMe_3)_2$	CPME	0
10	**P2**/5	LiO^tBu	DME	51
11	**P2**/5	LiO^tBu	dioxane	37
12	**P2**/5	LiO^tBu	THF	28
13[d]	**P2**/5	LiO^tBu	DME	61
14[e]	**P2**/5	LiO^tBu	DME	74 (70[f])

[a] Reaction performed using 1 equiv **3.1a**, 2 equiv **3.2a**, 3 equiv base at 80 °C on 0.1 mmol scale for 12 h. [b] Assay yield determined by ^{1}H NMR by using 0.1 mmol CH_2Br_2 as an internal standard. [c] 7.5 mol % NiXantPhos used. [d] 110 °C. [e] 24 h. [f] Isolated yield.

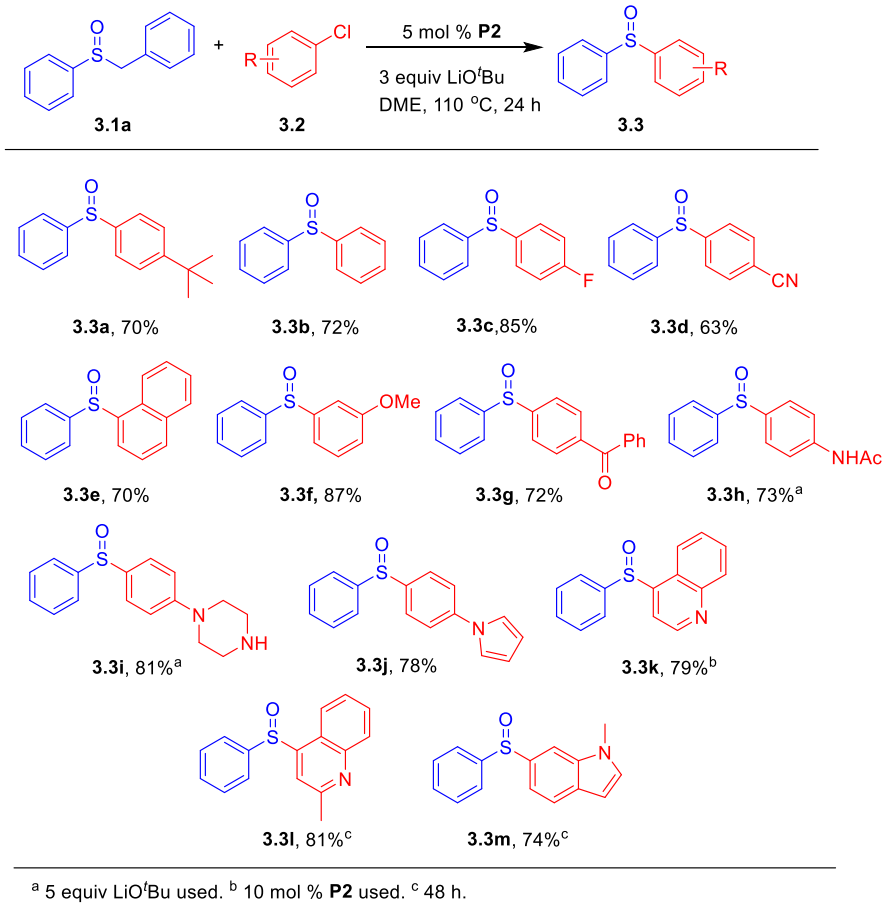


NiXantPhos **P1** **P2**

3.2.2 Substrate Scope of Aryl Chlorides in Palladium Catalyzed Diaryl Sulfoxide Generation from Aryl Benzyl Sulfoxides and Aryl Chlorides

With the optimized conditions for palladium-catalyzed cross-coupling of **3.1a** and **3.2a**, the substrate scope of aryl chlorides was investigated (Scheme 3-3). The parent diphenyl sulfoxide (**3.3b**) was generated from chlorobenzene (**3.2b**) in 72% yield. Aryl chlorides bearing electron-withdrawing groups, such as 4-F (**3.2c**) and 4-CN (**3.2d**), afforded the products in 85 and 63% yields, respectively. Both 1-chloro naphthalene (**3.2e**) and 3-chloro anisole (**3.2f**), were suitable cross-coupling partners under our optimal conditions, furnishing **3.3e** and **3.3f** in 70% and 87% yield,

respectively. 4-Chloro benzophenone was successfully coupled under the optimal conditions, delivering **3.3g** in 72% yield. We were surprised to find that our protocol could even accommodate aryl chlorides possessing active N–Hs, which might be expected to undergo Buchwald-Hartwig amination under basic conditions.[14] However, under the optimal conditions, acetamide **3.2h** and piperidine **3.2i** afforded products **3.3h** and **3i** in 73% and 81% yields respectively. The NiXantPhos ligated palladacyclic precursor successfully facilitated both C–C and C–S bond formation (Figure 3-1) faster than C–N bond formation, leaving N-H in both amide and amine intact. Hetrocyclic sulfoxides, which often exhibit bioactivities,[1] could also be prepared. Thus, 4-pyrrolephenyl phenyl sulfoxide (**3.3j**), 4-quinoline phenyl sulfoxide (**3.3k**), 2-methyl 4-quinoline phenyl sulfoxide (**3.3l**) and (*N*-methyl)-6-indolyl phenyl sulfoxide (**3.3m**) were generated in 74–81% yields.



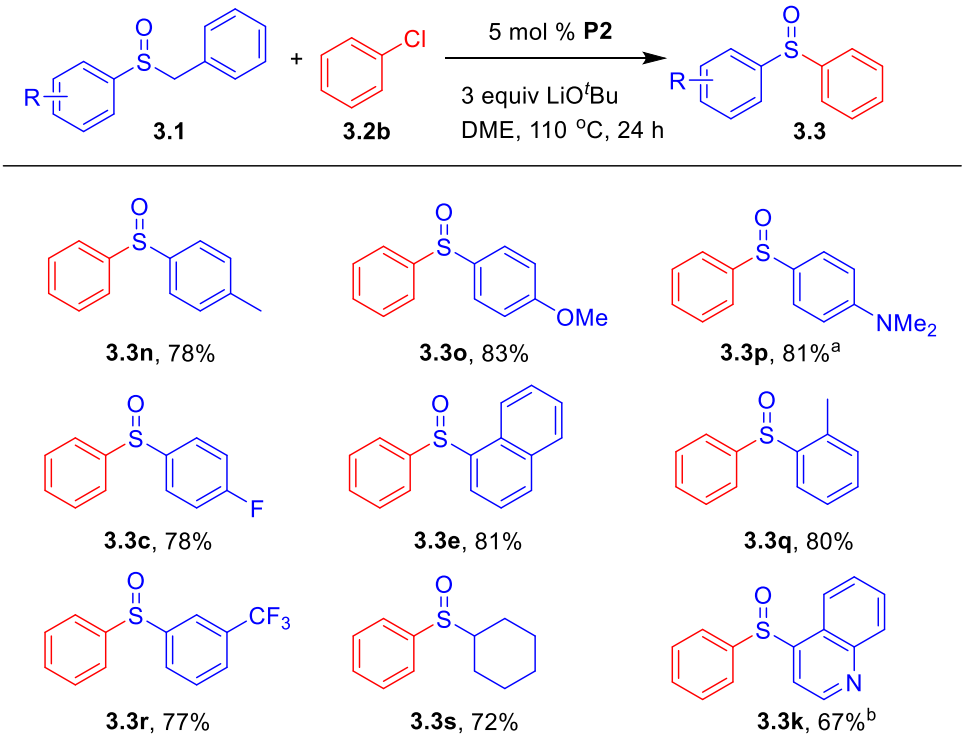
[a] 5 equiv LiO^{t}Bu used. [b] 10 mol % **P2** used. [c] 48 h.

Scheme 3-3. Substrate scope of aryl chlorides in palladium catalyzed diaryl sulfoxide formation

3.2.3 Substrate Scope of Aryl Benzyl Sulfoxides in Palladium Catalyzed Diaryl Sulfoxide Generation from Aryl Benzyl Sulfoxides and Aryl Chlorides

A variety of aryl benzyl sulfoxides were next explored in the presence of 5 mol % NiXantPhos ligated precatalyst **P2** (Scheme 3-4). Aryl benzyl sulfoxides bearing electron-donating groups furnished diaryl sulfoxides **3.3n**–**3.3p** in 78–83% yields. For reasons that remain unclear, 4-bromoanisole was not a viable substrate in our initial study.[9] In contrast, in the present case 4-chloro anisole afforded **3.3o** in 83% yield. Diaryl sulfoxides bearing electron-withdrawing 4-F or 3-CF_3 groups generated products in 77–78% yields. Sulfoxides bearing larger substituents, such as 1-naphthyl

(**3.1e**) and 2-tolyl (**3.1q**) were also viable coupling partners, providing **3.3e** and **3.3q** in 81–82% yield. Alkyl benzyl sulfoxides are more challenging substrates, because their α-C–H's are less acidic than aryl benzyl sulfoxides.[15] Nonetheless, cyclohexyl benzyl sulfoxide reacted with chlorobenzene to generate cyclohexyl phenyl sulfoxide (**3.3s**) in 72% yield. Heteroaryl benzyl sulfoxides are potentially useful coupling partners. The quinoline benzyl sulfoxide underwent coupling to provide the heteroaryl aryl sulfoxide **3.3k** in 67% yield with 10 mol % catalyst loading.

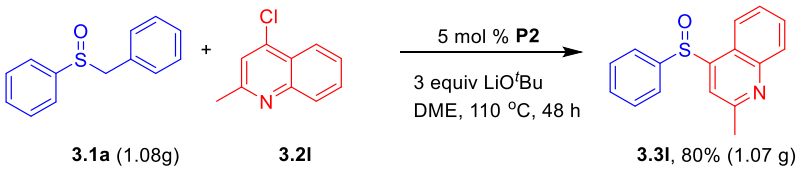


[a] 3 equiv PhCl used; [b] 10 mol % **P2** used.

Scheme 3-4. Substrate scope of aryl benzyl sulfoxides in palladium catalyzed diaryl sulfoxide formation

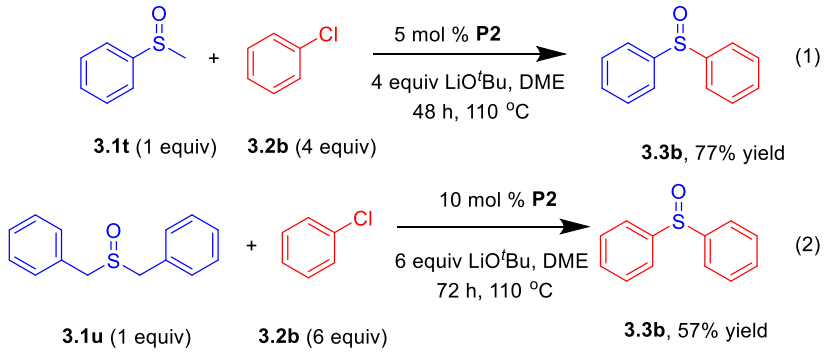
3.2.4 Gram Scale Synthesis of 3l and Expansion of Diaryl Sulfoxide Formation to Start from Benzyl Methyl Sulfoxide and Dibenzyl Sulfoxides

To demonstrate the potential utility of our method, we conducted a gram scale reaction with a heterocyclic aryl chloride (Scheme 3-5). Thus, phenyl benzyl sulfoxide (5 mmol, 1.08 g) was coupled with 4-chloro-2-methylquinoline (**3.2l**) in 80% yield (1.07 g).



Scheme 3-5. Gram scale synthesis of **3.3l** via palladium catalyzed diaryl sulfoxide generation

We next set out to evaluate different types of sulfoxides as precursors to diaryl sulfoxides. We previously demonstrated the arylation of aryl methyl sulfoxides to generate aryl benzyl sulfoxides,[12h] which are the substrates in the current study. Combining these two methods, we treated phenyl methyl sulfoxide with chlorobenzene under our standard conditions, giving diphenyl sulfoxide (**3.3b**), in 77% yield (Scheme 3-6). Likewise, dibenzyl sulfoxide (**3.1u**) and chlorobenzene (**3.2b**) could also be converted to diphenyl sulfoxide in 57% yield (Scheme 3-6B). Considering four C(sp^2)–Cl bonds have to be broken to generate each equivalent of **3.3b**, the moderate yield is reasonable.



Scheme 3-6. Preparation of diphenyl sulfoxide (**3.3b**) from methyl phenyl sulfoxide (**3.1u**) or dibenzyl sulfoxide (**3.1v**) and chlorobenzene (**3.2b**)

3.3 Conclusion

In summary, aryl chlorides have been utilized as electrophiles in the cross-coupling reactions with aryl benzyl sulfoxides to produce diaryl sulfoxides. A variety of functional groups, including those which might be expected to participate in related coupling reactions (Buchwald-Hartwig) or undergo addition reactions (C=O, CN), were well tolerated in our protocol. According to the proposed mechanism, C(sp^2)–Cl bond has to be cleaved twice to generate one molecule of product. To do so, an air and moisture stable NiXantPhos-derived palladacyclic precatalyst was applied as catalyst.

3.4 Experimental Section

General Methods: All reactions were carried out under dry nitrogen. Anhydrous CPME, dioxane, and dimethoxyethane (DME) were purchased from Sigma-Aldrich and directly used without further purification. THF was dried through activated alumina columns. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were purchased from

Sigma-Aldrich, Acros, Alfa Aesar, TCI or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wave ultraviolet light as well as by treatment with iodine. Flash chromatography was performed with silica gel (230–400 mesh, Silicycle). The NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in Hertz. The infrared spectra were taken with KBr plates with a Perkin-Elmer Spectrum 1600 Series spectrometer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Mel-Temp melting point apparatus and were uncorrected.

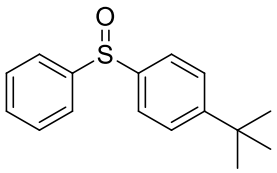
Preparation of Aryl Benzyl Sulfoxide: Sulfoxides were prepared according to the literature procedures.[16,17]

Preparation of Palladacyclic Precursors: Palladacyclic precursors were prepared according to the literature procedures.[13,14a]

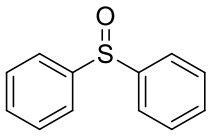
Procedure and Characterization for the Palladium Catalyzed Generation of Diaryl Sulfoxides.

General Procedure for catalysis: To an oven-dried microwave vial equipped with a stirbar was added **P2** (9.3 mg, 0.01 mmol), LiO^tBu (48.3 mg, 0.60 mmol, 3 equiv),

benzyl phenyl sulfoxide (43.2 mg, 0.20 mmol, 1 equiv) under nitrogen atmosphere in a glovebox. DME (2.0 mL) was added to the vial by syringe. The microwave vial was sealed, and removed from the glovebox. Then, 4-*tert*-butyl chlorobenzene (67.3 μL, 0.40 mmol, 2.0 equiv) was added by syringe under nitrogen atmosphere. Note that aryl chloride in a solid form was added to the reaction vial prior to LiO^tBu. The reaction mixture was heated to 110 ℃ in an oil bath and stirred for 24 h. Upon completion, the sealed vial was cooled to room temperature, and open to the air. The reaction mixture was passed through a short pad of silica gel, and rinsed with EtOAc. The solvent was removed under reduced pressure to yield a colorless solid. The residue was purified by flash chromatography as outlined below.

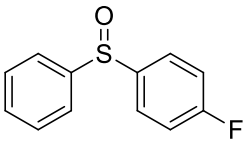


1-(*tert*-Butyl)-4-(phenylsulfinyl)benzene (3.3a): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 4-*tert*-butyl chlorobenzene (**3.2a**) (67.3 μL, 0.40 mmol) at 110 °C for 24 h.. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (36.2 mg, 70% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

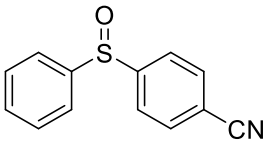


Diphenyl sulfoxide (3.3b): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 °C for 24 h. The crude product was

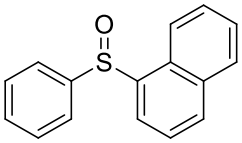
purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (29.1 mg, 72% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]



1-Fluoro-4-(phenylsulfinyl)benzene (3.3c): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 1-chloro-4-fluorobenzene (**3.2c**) (42.6 μL, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (37.4 mg, 85% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

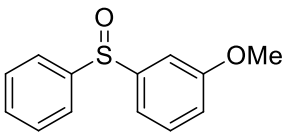


4-(Phenylsulfinyl)benzonitrile (3.3d): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 4-chlorobenzonitrile (**3.2d**) (55.0 mg, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (28.6 mg, 63% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[18]

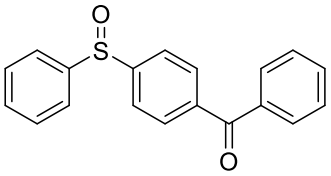


1-(Phenylsulfinyl)naphthalene (3.3e): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60

mmol) in 2.0 mL of DME, and 1-chloronaphthalene (**3.2e**) (54.5 μL, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:5) to give the product (35.3 mg, 70% yield) as a white solid. R_f = 0.5 (hexanes:EtOAc = 4:1). The spectroscopic data match the previously reported data.[9]

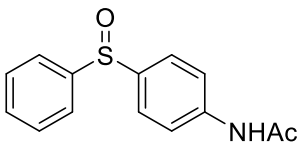


1-Methoxy-3-(phenylsulfinyl)benzene (3.3f): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 3-chloroanisole (**3.2f**) (49.0 μL, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (40.4 mg, 87% yield) as a white solid. R_f = 0.3 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

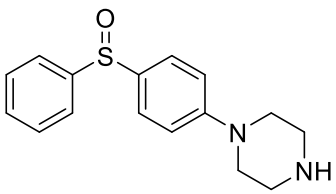


Phenyl(4-(phenylsulfinyl)phenyl)methanone (3.3g): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 4-chlorobenzophenone (**3.2g**) (86.7 mg, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:10) to give the product (44.1 mg, 72% yield) as a white solid. R_f = 0.5 (hexanes:EtOAc = 2:1); m.p. = 77–79 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8 Hz, 2H), 7.74 (d, *J* = 8 Hz, 4H), 7.68 – 7.66 (m, 2H), 7.58 (t, *J* = 7.5 Hz,

1H), 7.47 – 7.44 (m, 5H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 195.5, 149.9, 145.1, 139.8, 136.8, 132.9, 131.5, 130.7, 130.0, 129.6, 128.5, 124.9, 124.4 ppm; IR (thin film): 1660, 1590, 1441, 1394, 1317, 1305, 1276, 1090, 1048, 924, 700, 660 cm^{-1}; HRMS calculated for $C_{19}H_{15}O_2S$ 307.0793, found 307.0786 $[M+H]^+$.

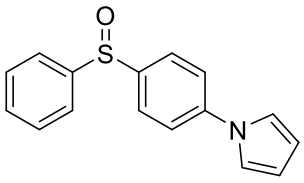


***N*-(4-(phenylsulfinyl)phenyl)acetamide (3.3h):** The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (80.0 mg, 1.00 mmol) in 2.0 mL of DME, and 4'-chloroacetanilide (**3.2h**) (67.8 mg, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:1) to give the product (37.8 mg, 73% yield) as a white solid. R_f = 0.2 (hexanes:EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.57 – 7.55 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.41 (m, 3H), 2.10 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 169.2, 144.9, 141.4, 139.2, 131.1, 129.3, 126.2, 124.6, 120.3, 24.4 ppm; IR (thin film): 3265, 1696, 1678, 1590, 1533, 1398, 1314, 1260, 1089, 1032, 833, 749 cm^{-1}; HRMS calculated for $C_{14}H_{13}O_2SN$ 260.0745, found 260.0743 $[M+H]^+$. Melting point was previously reported.[19]

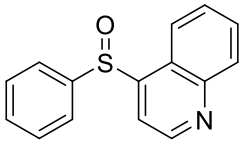


1-(4-(Phenylsulfinyl)phenyl)piperazine (3.3i): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (80.0 mg, 1.00 mmol) in 2.0 mL DME, and 4'-chloroacetanilide (**3.2i**) (67.8 mg, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash

chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (37.8 mg, 73% yield) as a white solid. m.p. = 80–82 ℃; R_f = 0.4 (hexanes:EtOAc = 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 6 Hz, 2H), 7.53 –7.50 (m, 3H), 7.31 (d, *J* = 9 Hz, 2H), 6.74 (d, *J* = 9 Hz, 2H), 3.31 –3.12 (m, 8H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.0, 142.6, 131.9, 131.1, 128.9, 126.2, 118.2, 112.6, 49.6, 45.6 ppm; IR (thin film): 2920, 2451, 1498, 1455, 1349, 1254, 1149, 810, 752, 699 cm^{-1}; HRMS calculated for $C_{16}H_{19}OSN_2$ 287.1218, found 287.1424 $[M+H]^+$.

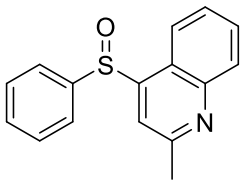


1-(4-(Phenylsulfinyl)phenyl)-1H-pyrrole (3.3j): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^{t}Bu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 1-(4-chlorophenyl)-1H-pyrrole (**3.2j**) (67.8 mg, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (41.7 mg, 78% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 4:1). m.p. = 104–106 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 – 7.64 (m, 4H), 7.49 – 7.44 (m, 5H), 7.06 (d, *J* = 4.5 Hz, 2H), 6.34 (d, *J* = 4.5 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 145.4, 142.8, 142.1, 131.2, 129.4, 126.5, 124.7, 120.7, 119.1, 111.4 ppm; IR (thin film): 1596, 1510, 1331, 1089, 1047, 919, 824, 726 cm^{-1}; HRMS calculated for $C_{16}H_{14}OSN$ 268.0796, found 268.0793 $[M+H]^+$.



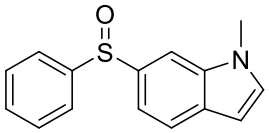
4-(Phenylsulfinyl)quinoline (3.3k): The reaction was performed following the General Procedure with **P2** (18.6 mg, 0.02 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^{t}Bu (48.0 mg, 0.60

mmol) in 2.0 mL of DME, and 4-chloroquinoline (**3.2k**) (65.4 mg, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (40.0 mg, 79% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 4:1). m.p. = 88–90 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, *J* = 2.0 Hz, 1H), 8.61 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.81 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.74 – 7.72 (m, 2H), 7.65 (dt, , *J* = 7.8, 1.5 Hz, 1H), 7.51 – 7.48 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 148.8, 145.9, 144.5, 138.9, 133.0, 131.7, 131.4, 129.7, 129.6, 128.5, 128.0, 127.3, 125.0 ppm; IR (thin film): 3057, 1581, 1565, 1494, 1443, 1358, 1086, 1048, 786, 749, 689 cm^{-1}; HRMS calculated for $C_{15}H_{12}OSN$ 254.0640, found 254.0639 $[M+H]^+$.

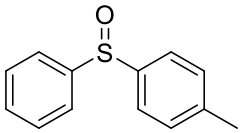


2-Methyl-4-(phenylsulfinyl)quinoline (3.3l): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 4-chloro-2-methyl quinoline (**3.2l**) (71.1 mg, 0.40 mmol) at 110 ℃ for 48 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (43.3 mg, 81% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 4:1). m.p. = 139–141 ℃; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.67 (m, 3H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.41 – 7.39 (m, 3H), 2.82 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.4, 151.4, 148.0, 143.8, 131.8, 130.1, 129.7, 129.6, 126.7, 125.7, 122.1, 121.9, 117.1, 25.7 ppm; IR (thin film): 2922, 1587, 1555, 1497, 1442, 1401, 1080, 1052, 756, 690 cm^{-1}; HRMS calculated for

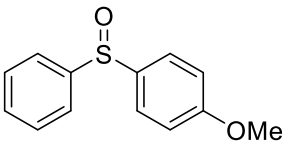
$C_{16}H_{14}OSN$ 268.0796, found 268.0814 $[M+H]^+$.



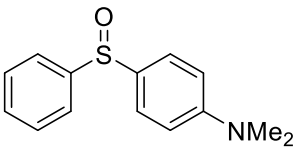
1-Methyl-6-(phenylsulfinyl)-1*H*-indole (3.3m): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1a** (43.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and 6-chloro-1-methyl-1*H*-indole (**3.2m**) (66.2 mg, 0.40 mmol) at 110 ℃ for 48 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (37.7 mg, 74% yield) as a colorless vicious oil. R_f = 0.4 (hexanes:EtOAc = 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.65 – 7.61 (m, 3H), 7.43 – 7.38 (m, 3H), 7.17 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 146.4, 138.0, 136.3, 131.3, 130.7, 130.6, 129.1, 124.8, 121.7, 115.9, 106.7, 101.5, 33.1 ppm; IR (thin film): 2925, 1506, 1473, 1442, 1339, 1302, 1081, 1039, 809, 748, 733, 689 cm^{-1}; HRMS calculated for $C_{15}H_{14}OSN$ 256.0796, found 256.0788 $[M+H]^+$.



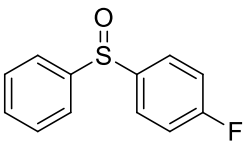
1-Methyl-4-(phenylsulfinyl)benzene (3.3n): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1n** (46.1 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (33.7 mg, 78% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]



1-Methoxyl-4-(phenylsulfinyl)benzene (3.3o): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1o** (49.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:2) to give the product (38.5 mg, 83% yield) as a white solid. R_f = 0.2 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[19]

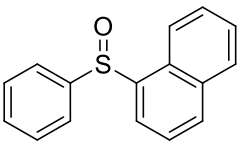


***N,N*-dimethyl-4-(phenylsulfinyl)aniline (3.3p):** The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1p** (51.8 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (60.9 μL, 0.60 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:1) to give the product (39.7 mg, 81% yield) as a white solid. R_f = 0.2 (hexanes:EtOAc = 1:1). The spectroscopic data match the previously reported data.[9]

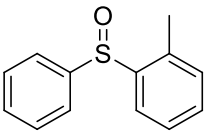


1-Fluoro-4-(phenylsulfinyl)benzene (3.3c) (from 1-(benzylsulfinyl)-4-fluorobenzene): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), **3.1c** (46.8 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with

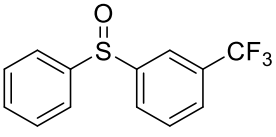
EtOAc:hexanes = 1:4) to give the product (34.3 mg, 78% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]



1-(Phenylsulfinyl)naphthalene (3.3e) (from 1-(benzylsulfinyl)naphthalene): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), 1-(benzylsulfinyl)naphthalene (**3.1e**) (53.2 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (41.3 mg, 81% yield) as a white solid. R_f = 0.5 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

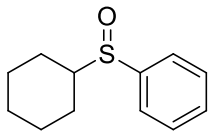


1-Methyl-2-(phenylsulfinyl)benzene (3.3q): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), 1-(benzylsulfinyl)-2-methylbenzene (**3.1q**) (46.0 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (34.6 mg, 80% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

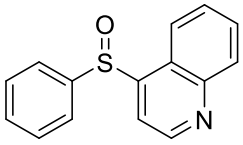


1-(Phenylsulfinyl)-3-(trifluoromethyl)benzene (3.3r): The reaction was performed following the General Procedure with

P2 (9.3 mg, 0.01 mmol), 1-(benzylsulfinyl)-3-(trifluoromethyl)benzene (**3.1r**) (56.8 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 °C for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (41.6 mg, 77% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.64 – 7.63 (m, 3H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.47 – 7.44 (m, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.2, 144.8, 132.1(q, *J* = 33.3 Hz), 131.6, 129.9, 129.6, 127.8, 127.6 (q, *J* = 4.8 Hz), 124.7, 123.3 (q, *J* = 271.5 Hz), 121.4 (q, *J* = 3.8 Hz) ppm; IR (thin film): 3055, 2924, 1580, 1476, 1443, 1090, 1045, 1021, 997, 742, 694 cm^{-1}; HRMS calculated for $C_{13}H_{10}OSF_3$ 271.0404, found 271.0406 $[M+H]^+$. Melting point was previously reported.[20]

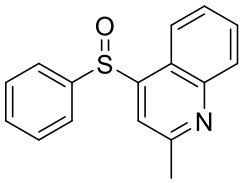


(Cyclohexylsulfinyl)benzene (3.3s): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), ((cyclohexylsulfinyl)methyl)benzene (**3.1s**) (44.4 mg, 0.20 mmol), LiO^tBu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:2) to give the product (37.2 mg, 72% yield) as a pale yellow solid. R_f = 0.1 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

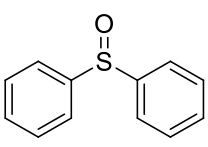


4-(Phenylsulfinyl)quinoline (3.3k) (from 4-(benzylsulfinyl)quinoline)): The reaction was performed

following the General Procedure with **P2** (18.6 mg, 0.02 mmol), 4-(benzylsulfinyl)quinoline (**3.1k**) (53.5 mg, 0.20 mmol), LiO^{t}Bu (48.0 mg, 0.60 mmol) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (40.6 μL, 0.40 mmol) at 110 ℃ for 24 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (33.9 mg, 67% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 4:1).

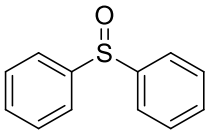


2-Methyl-4-(phenylsulfinyl)quinoline (3.3l) (5 mmol scale): To an oven-dried Schlenk flask equipped with a stirbar was added **P2** (231.5 mg, 0.5 mmol), LiO^{t}Bu (1.2 g, 15.0 mmol, 3 equiv), benzyl phenyl sulfoxide (1.08 g, 5.0 mmol, 1 equiv), 4-chloro-2-methyl quinoline (**3.2l**) (1.78 g, 10.0 mmol, 2 equiv) at 110 ℃ for 24 h under a nitrogen atmosphere in a glovebox. DME (50.0 mL) was added to the vial by syringe. The Schlenk flask was sealed and removed from the glovebox. Then, it was equipped with a condenser under a nitrogen atmosphere. The reaction mixture was heated to 110 ℃ in an oil bath and stirred for 24 h. Upon completion, the Schlenk flask was cooled to room temperature, and open to the air. The reaction mixture was passed through a short pad of silica gel, and rinsed with EtOAc. The solvent was removed under reduced pressure to yield a colorless solid (1.07 g, 80%). R_f = 0.4 (hexanes:EtOAc = 4:1).



Diphenyl sulfoxide (3.3b) (from methyl phenyl sulfoxide): The reaction was performed following the General Procedure with **P2** (9.3 mg, 0.01 mmol), methyl phenyl sulfoxide (**3.1t**) (28.0 mg, 0.20 mmol), LiO^{t}Bu

(64.0 mg, 0.80 mmol, 4 equiv) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (81.2 μL, 0.80 mmol, 4 equiv) at 110 ℃ for 48 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (31.1 mg, 77% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]



Diphenyl sulfoxide (3.3b) (from dibenzyl sulfoxide): The reaction was performed following the General Procedure with **P2** (18.6 mg, 0.02 mmol), diphenyl sulfoxide (**3.1u**) (46.0 mg, 0.20 mmol), LiO^tBu (96.0 mg, 1.20 mmol, 6 equiv) in 2.0 mL of DME, and chlorobenzene (**3.2b**) (121.8 μL, 1.20 mmol, 6 equiv) at 110 ℃ for 72 h. The crude product was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 1:4) to give the product (23.0 mg, 57% yield) as a white solid. R_f = 0.4 (hexanes:EtOAc = 2:1). The spectroscopic data match the previously reported data.[9]

3.5 References

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Appendix A1. NMR Spectra Relevant to Chapter 1

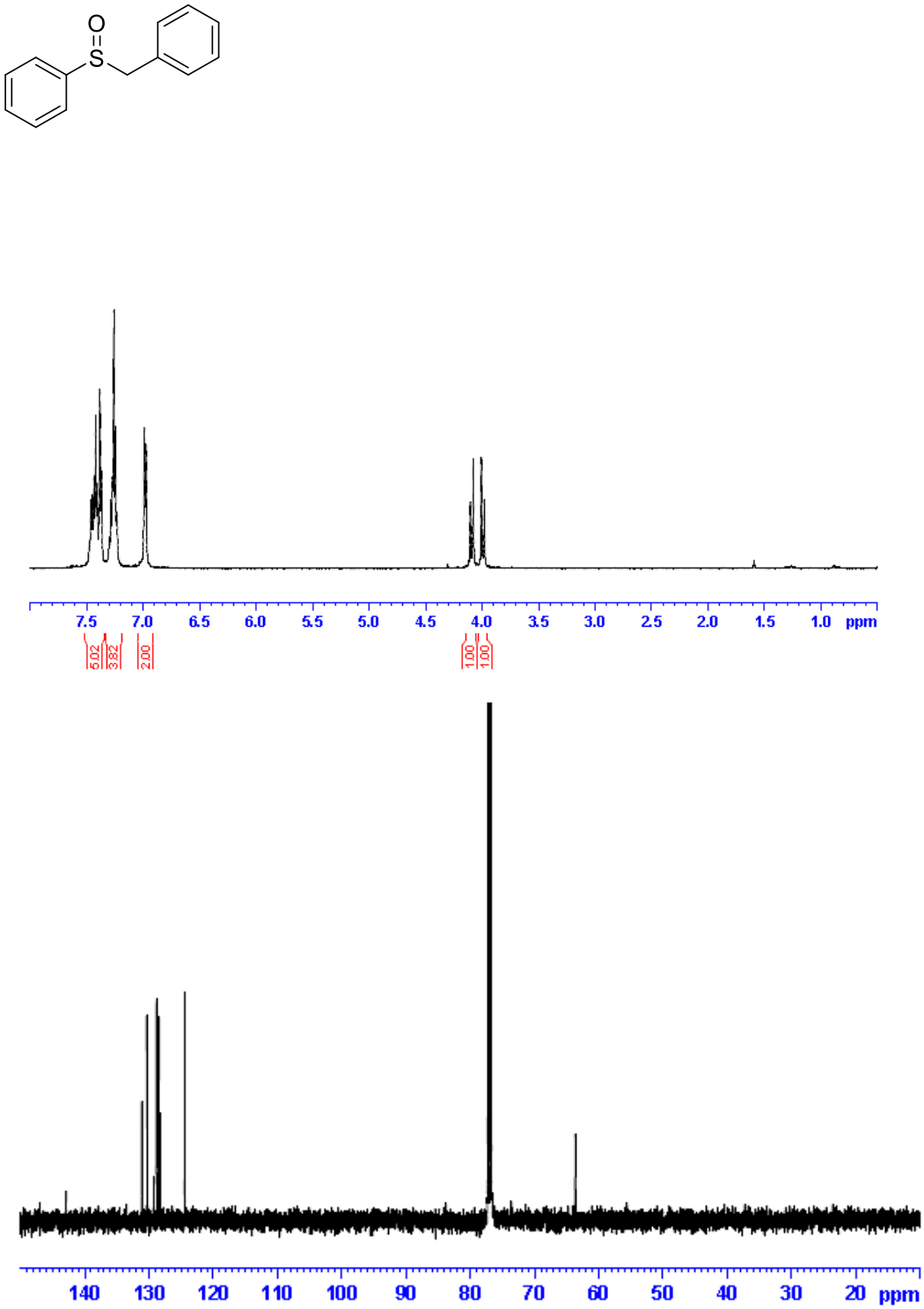
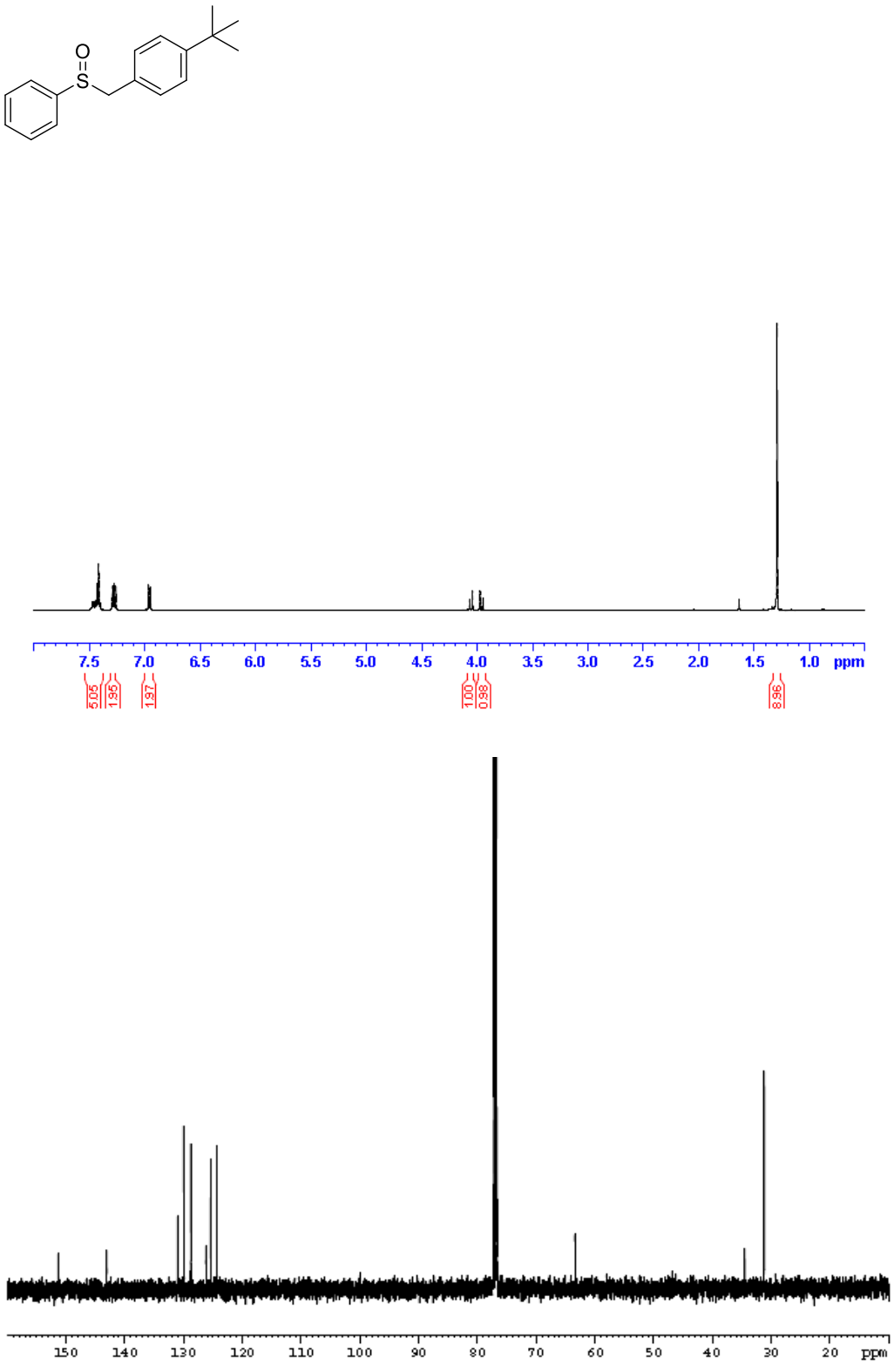


Figure A1.1 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3a** in $CDCl_3$



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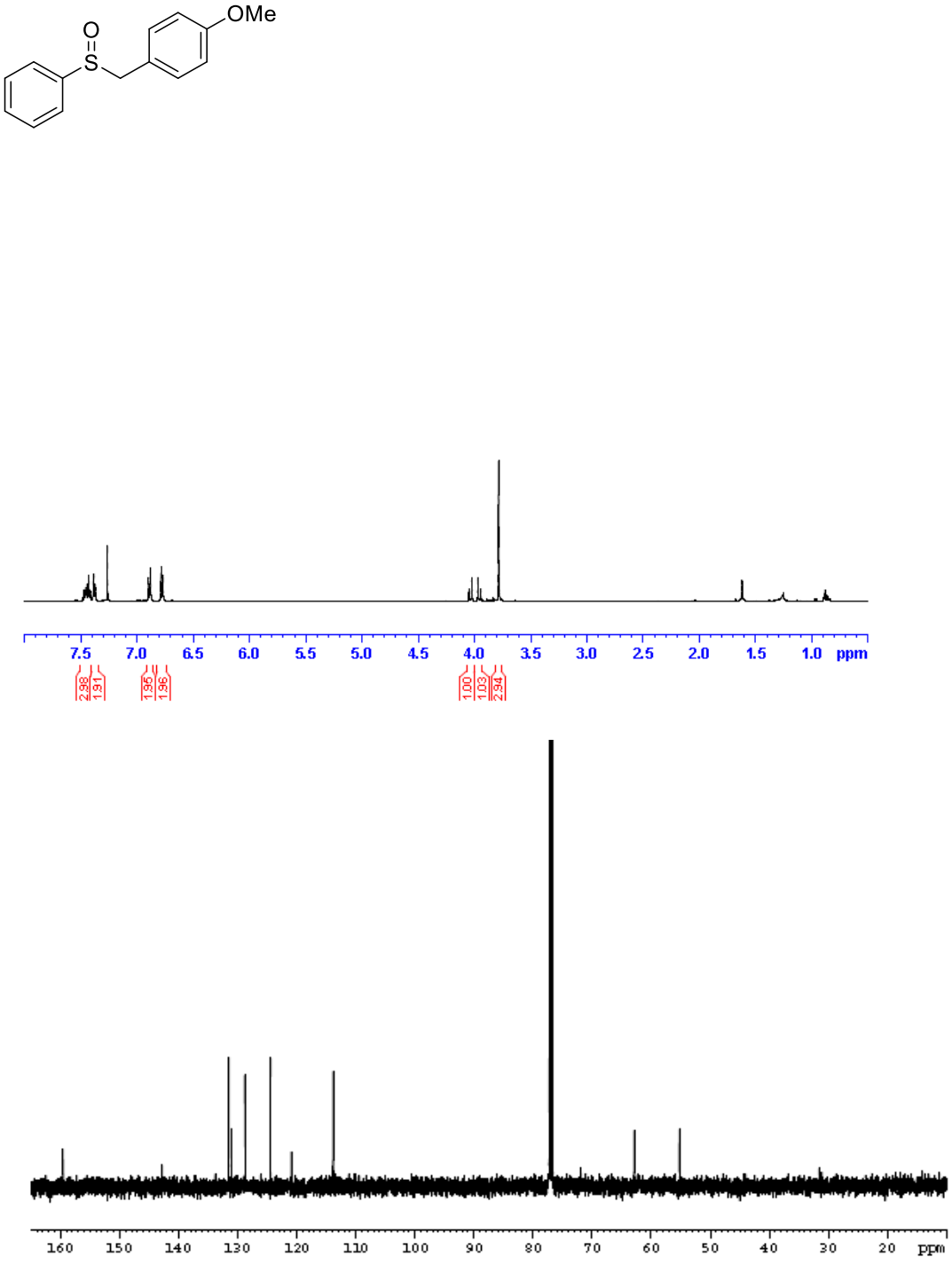


Figure A1.3 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3c** in $CDCl_3$

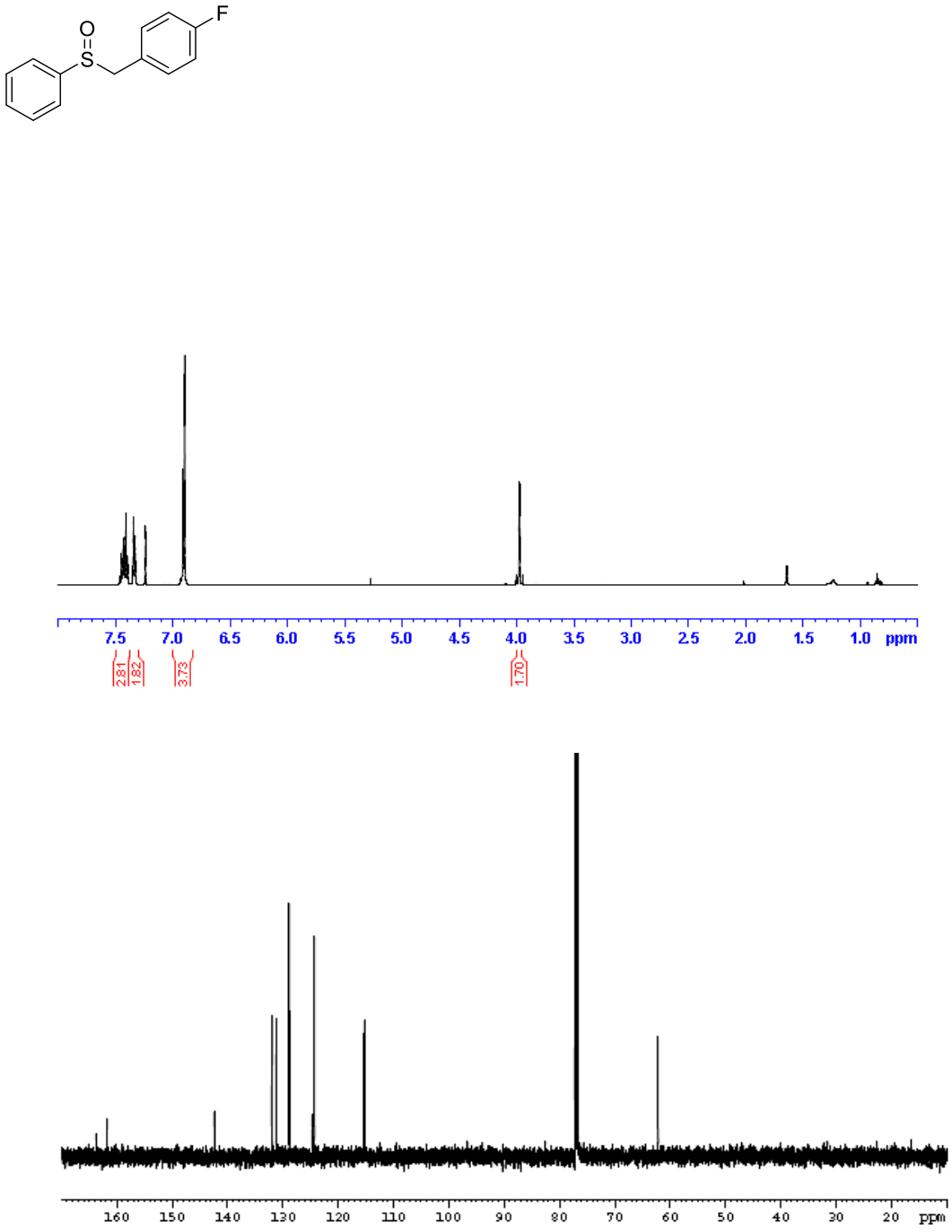


Figure A1.4 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3d** in $CDCl_3$

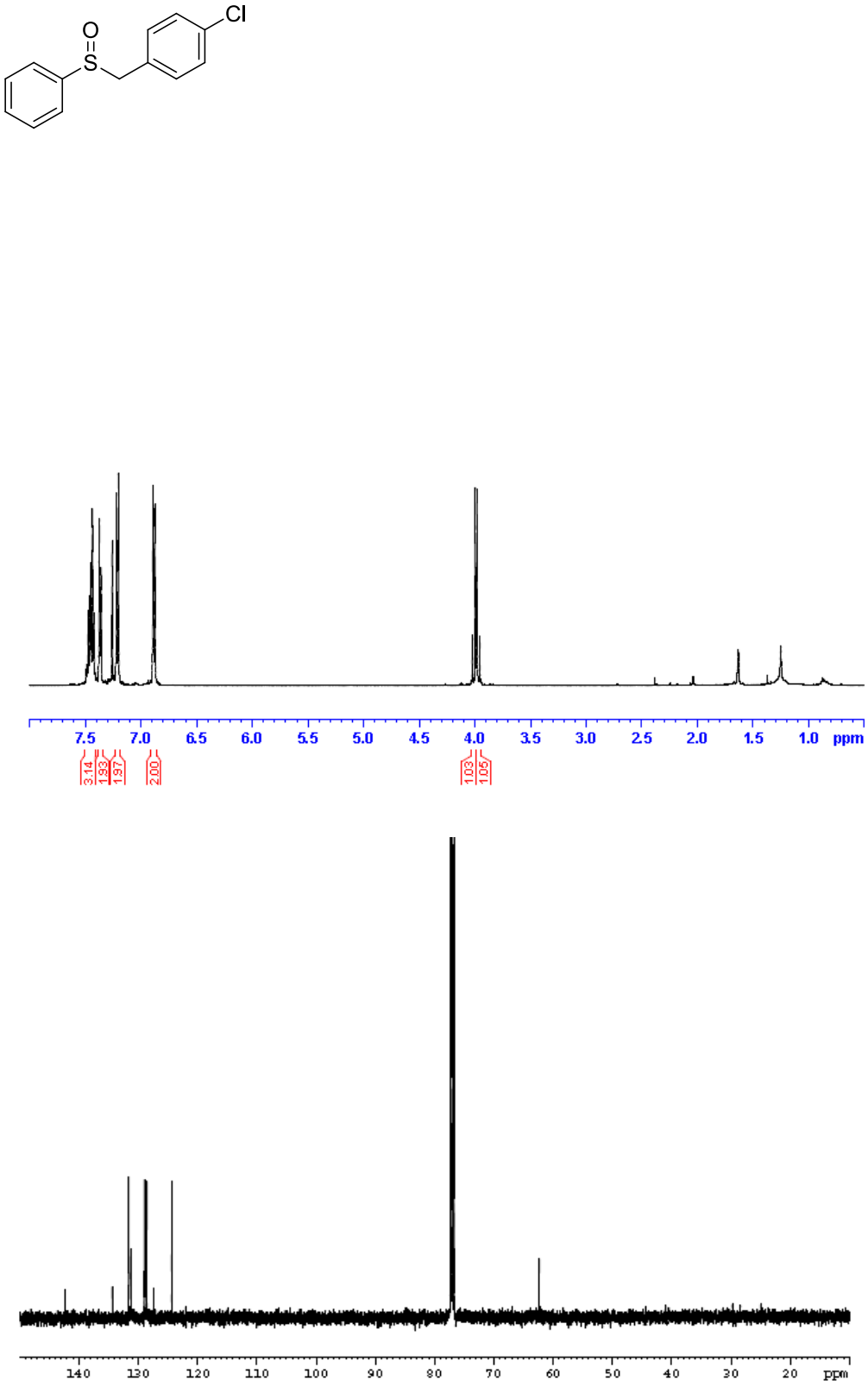


Figure A1.5 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3e** in $CDCl_3$

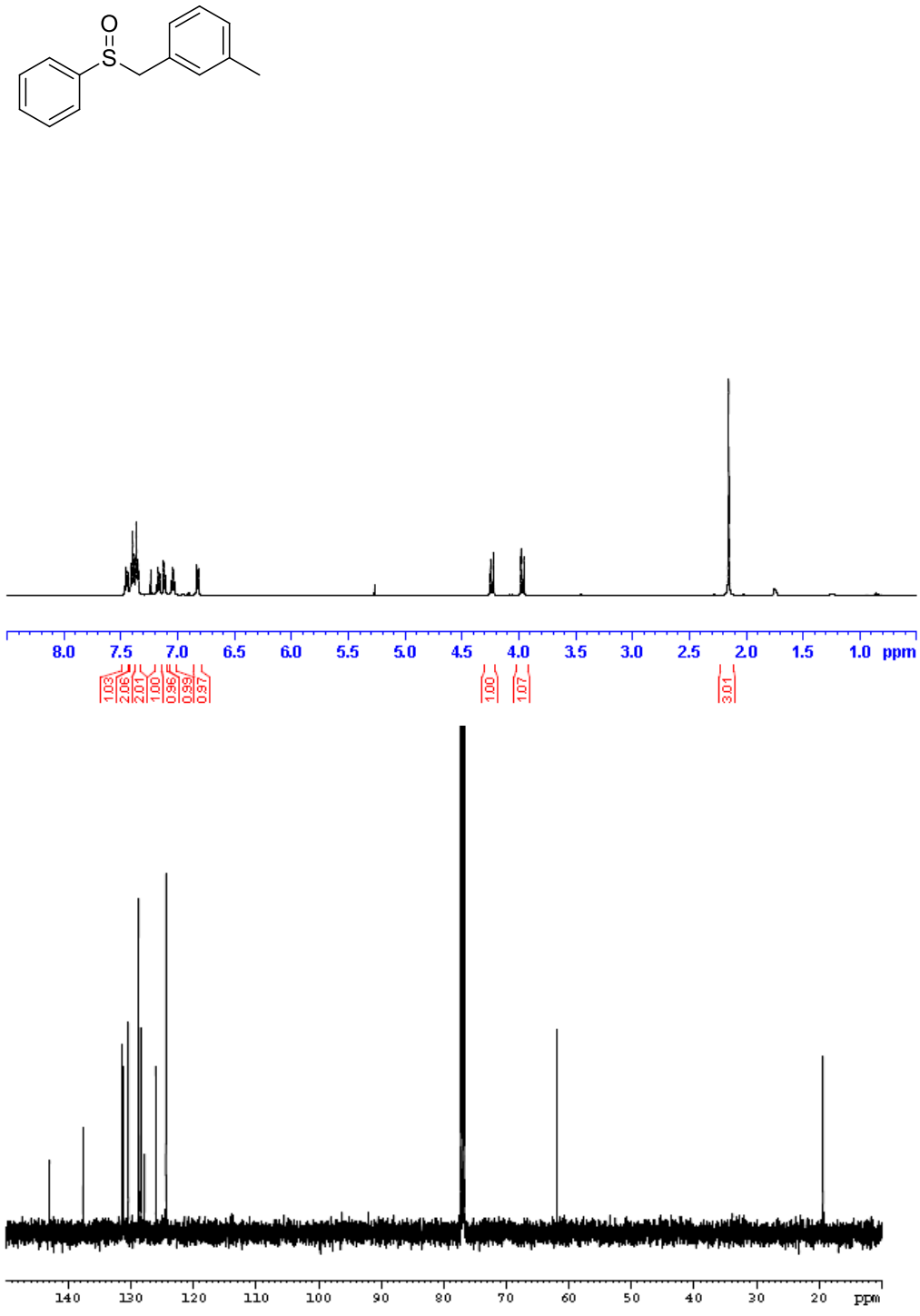
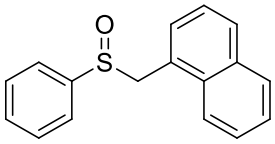
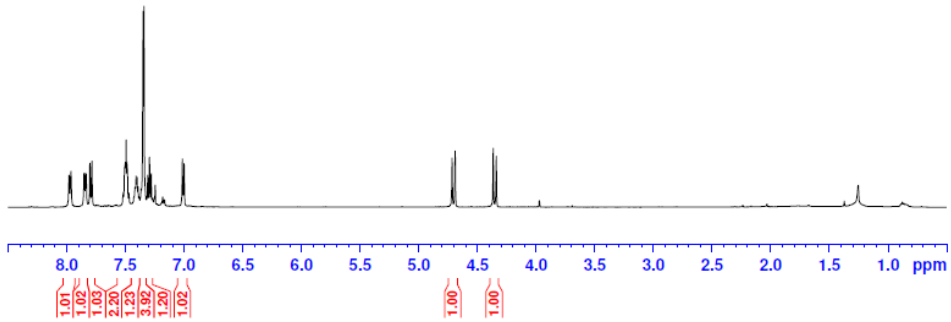


Figure A1.6 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3f** in $CDCl_3$





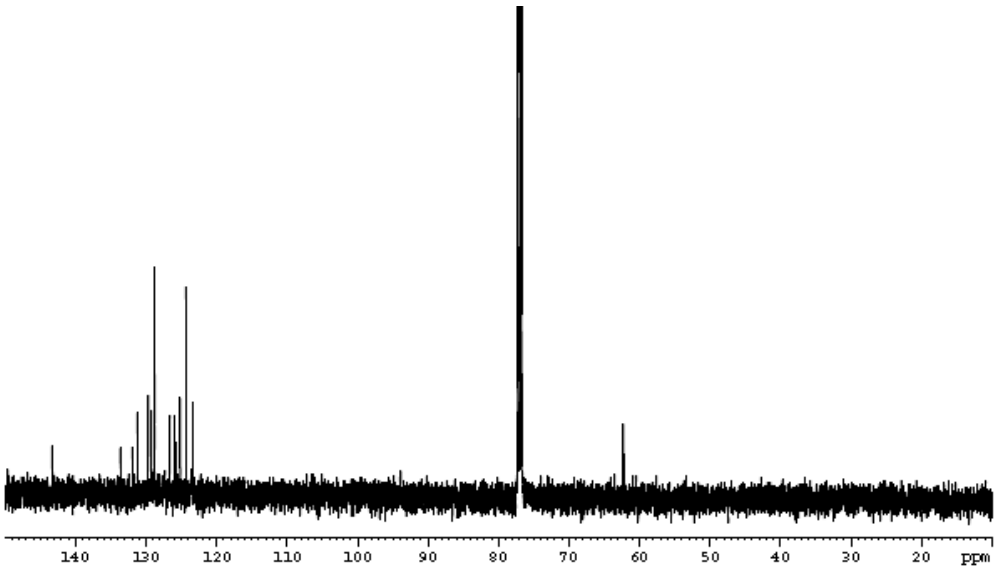


Figure A1.7 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3g** in $CDCl_3$

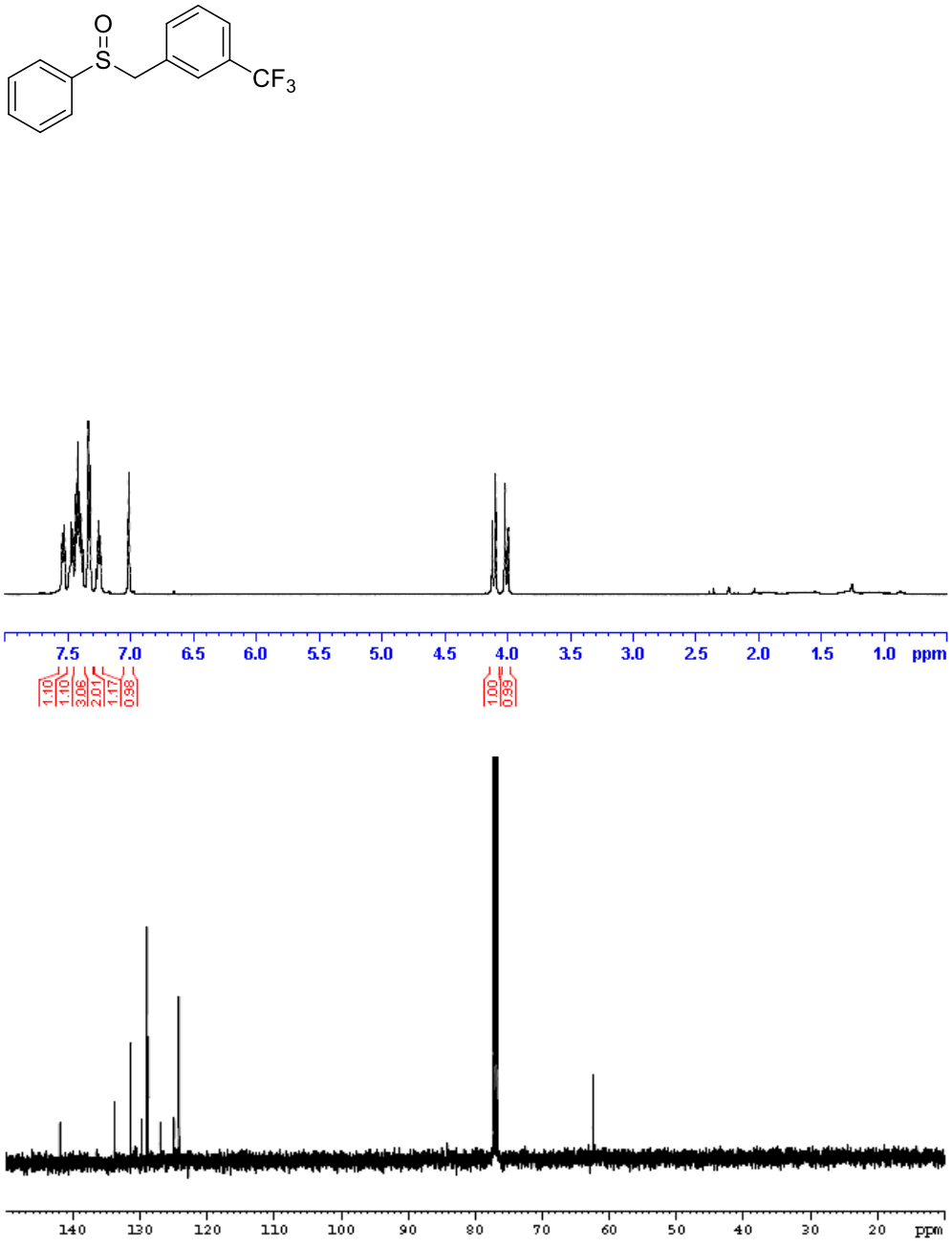
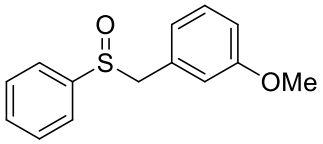


Figure A1.8 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3h** in $CDCl_3$



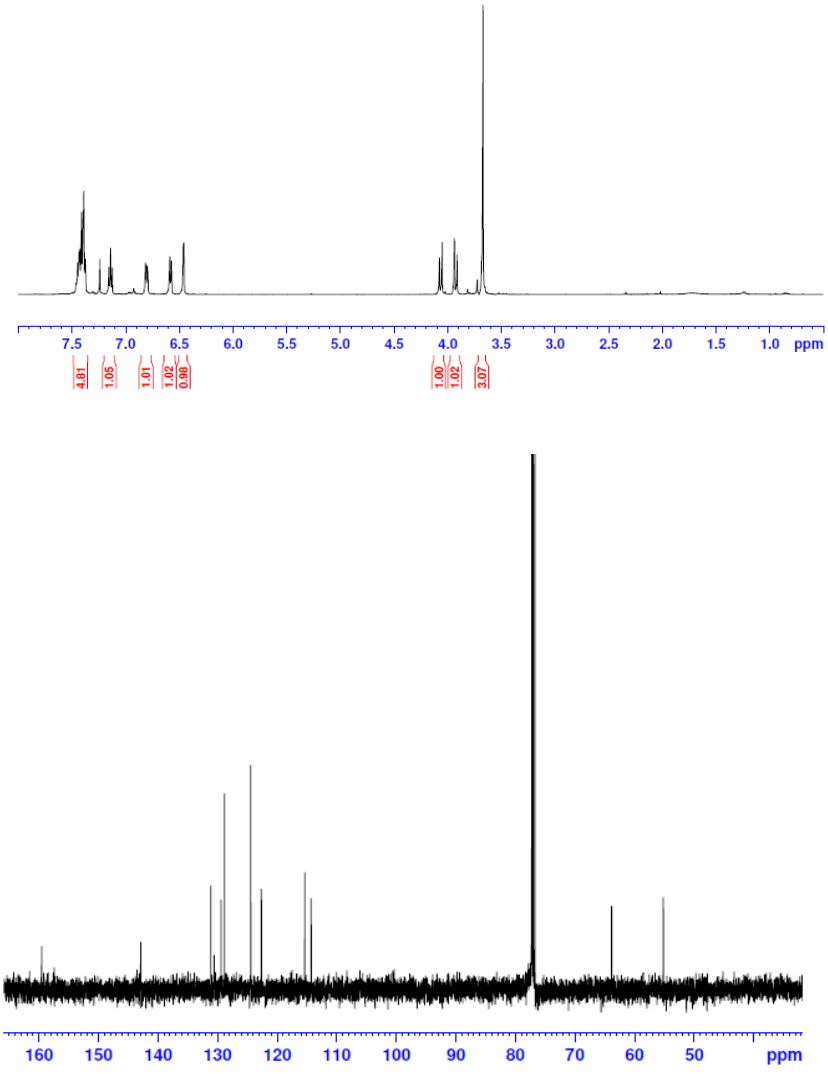


Figure A1.9 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.3i** in $CDCl_3$

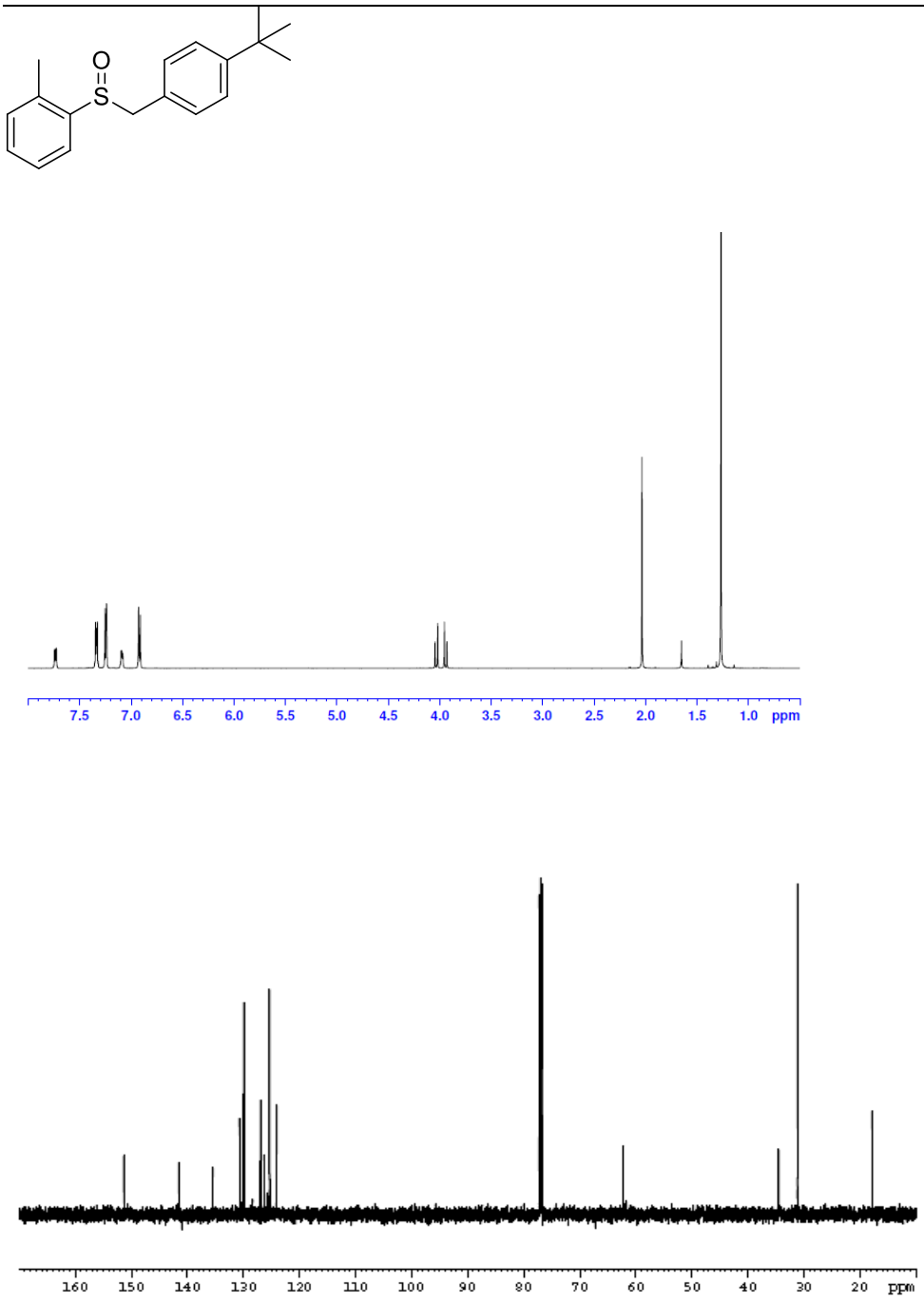


Figure A1.10 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4a** in $CDCl_3$

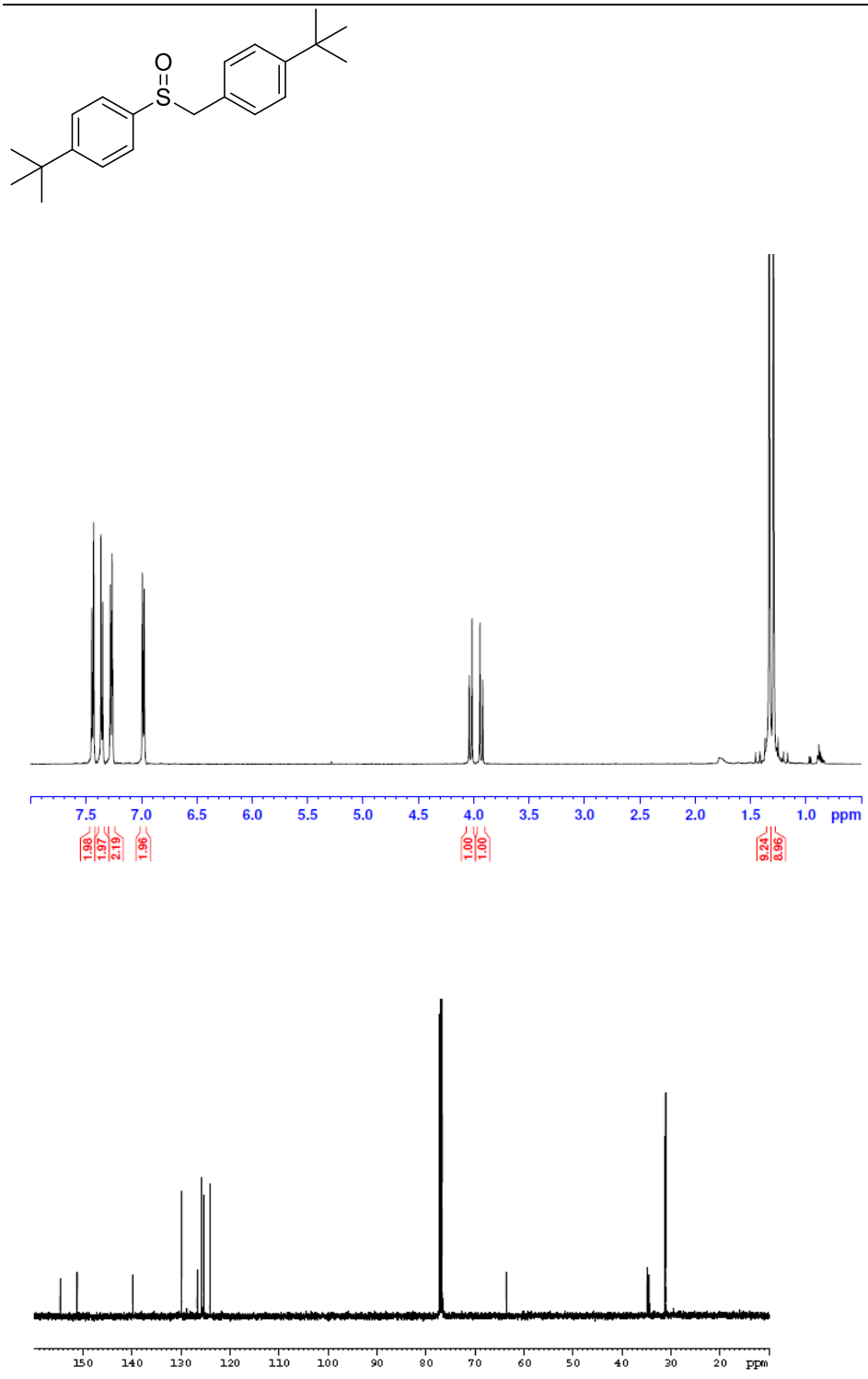


Figure A1.11 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4b** in $CDCl_3$

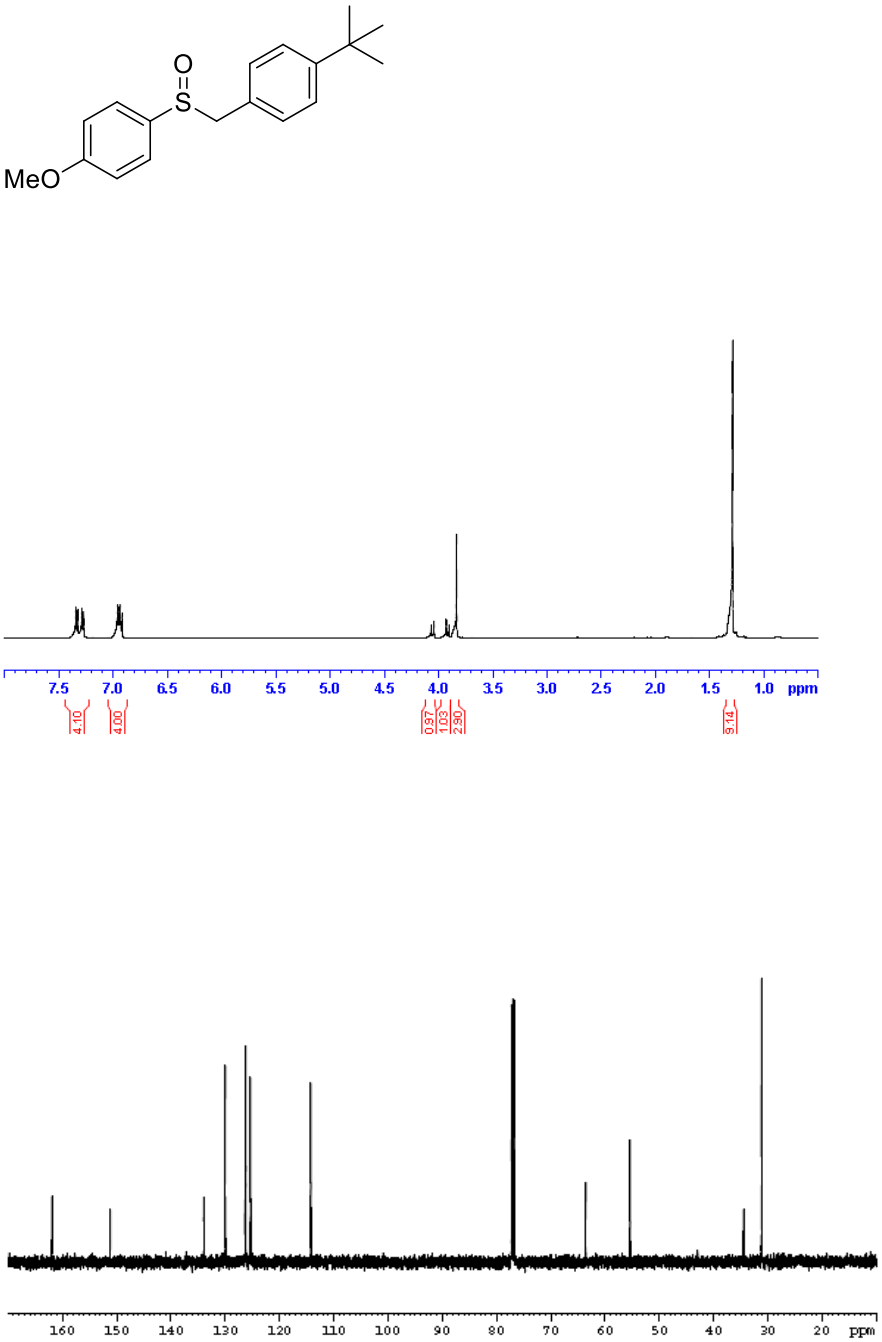


Figure A1.12 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4c** in $CDCl_3$

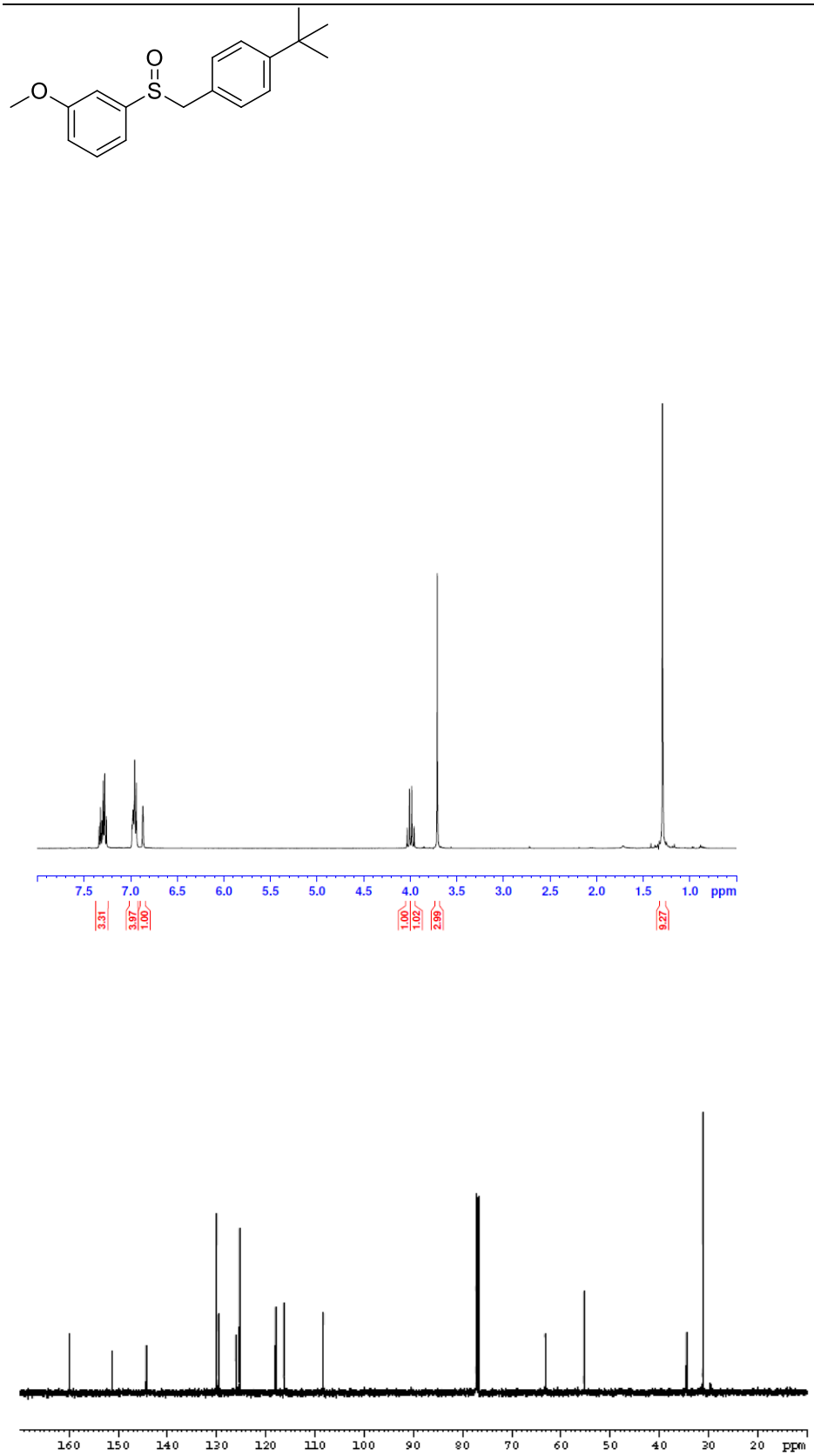


Figure A1.13 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4d** in $CDCl_3$

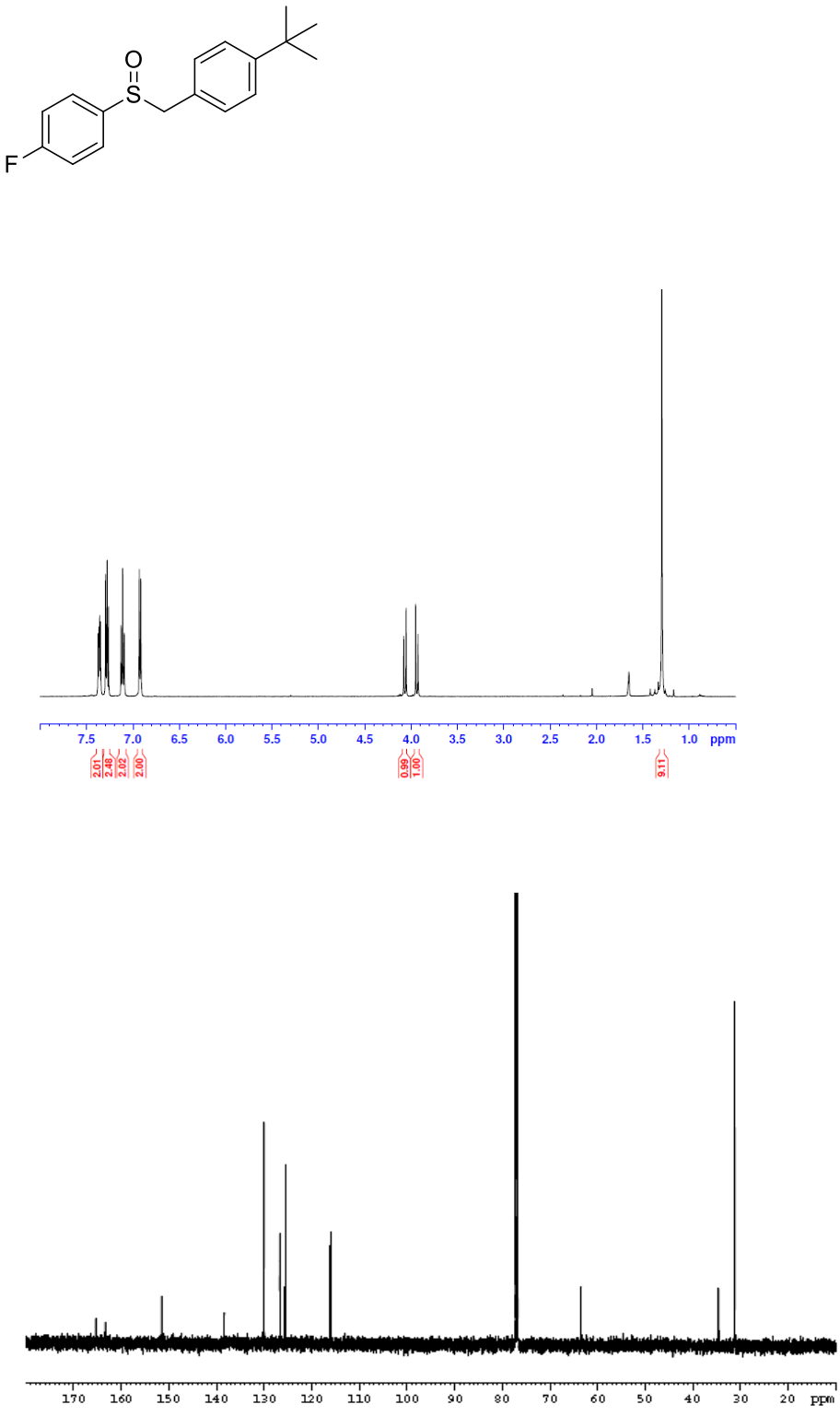


Figure A1.14 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4e** in $CDCl_3$

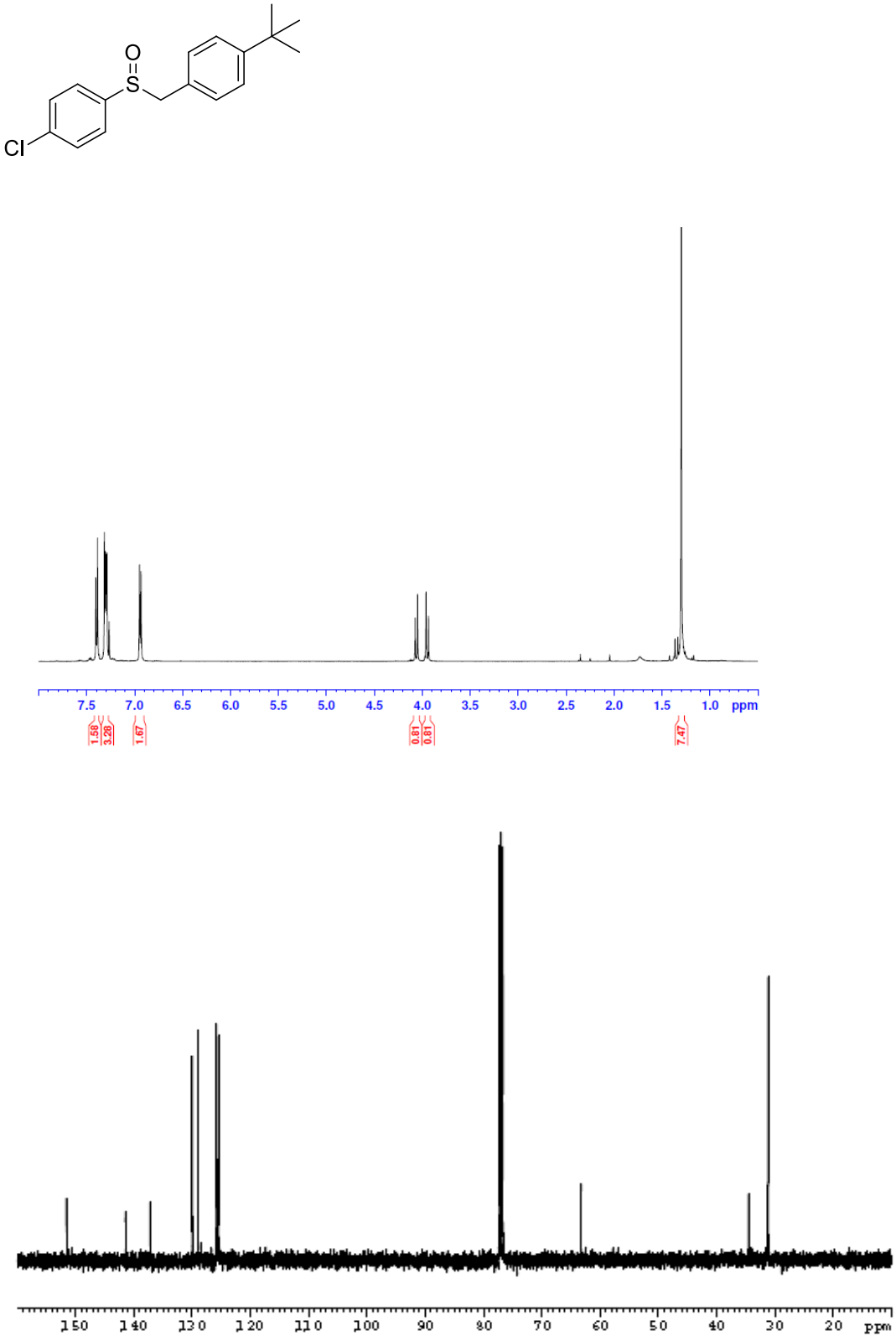


Figure A1.15 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4f** in $CDCl_3$

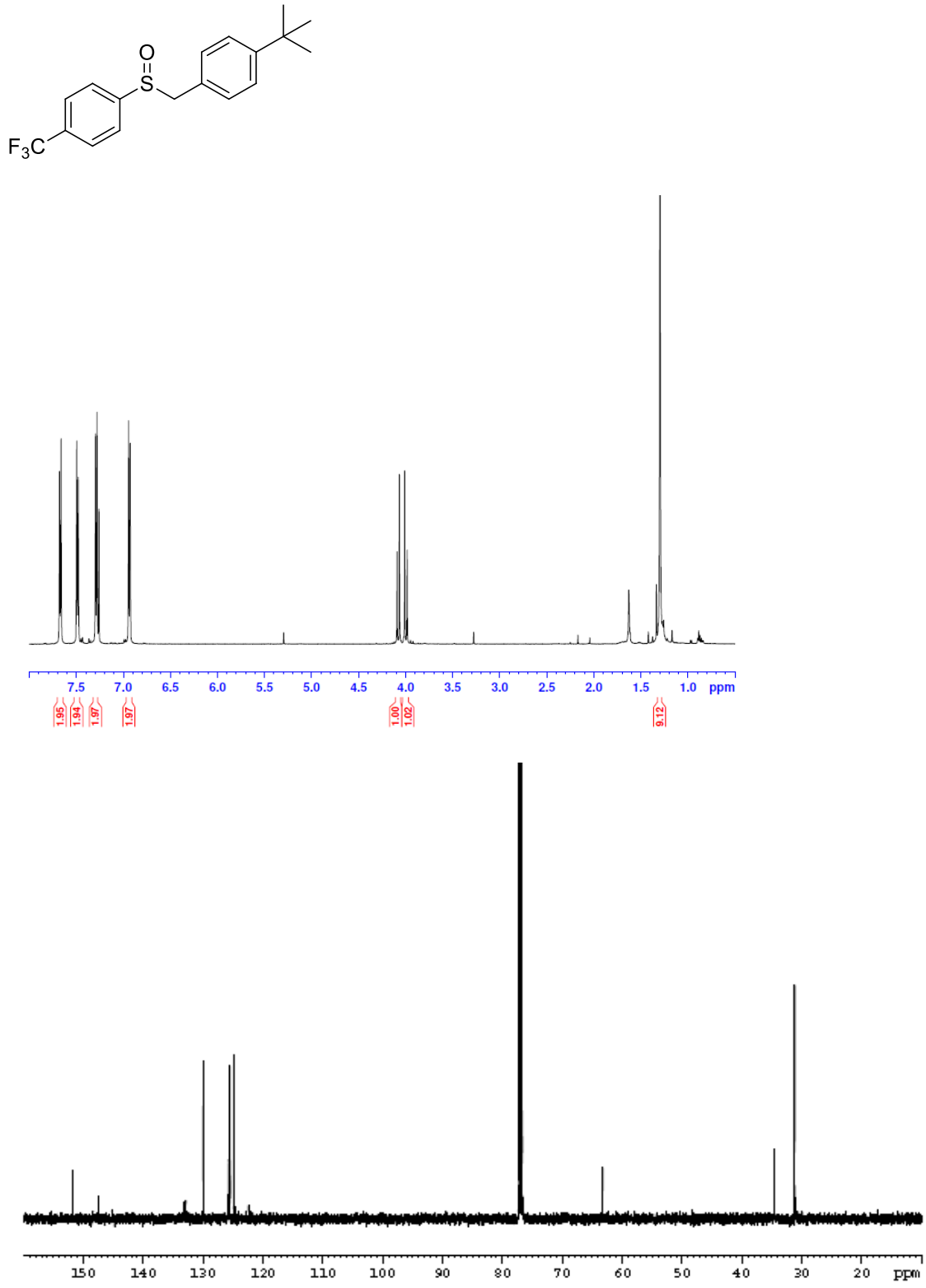


Figure A1.16 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4g** in $CDCl_3$

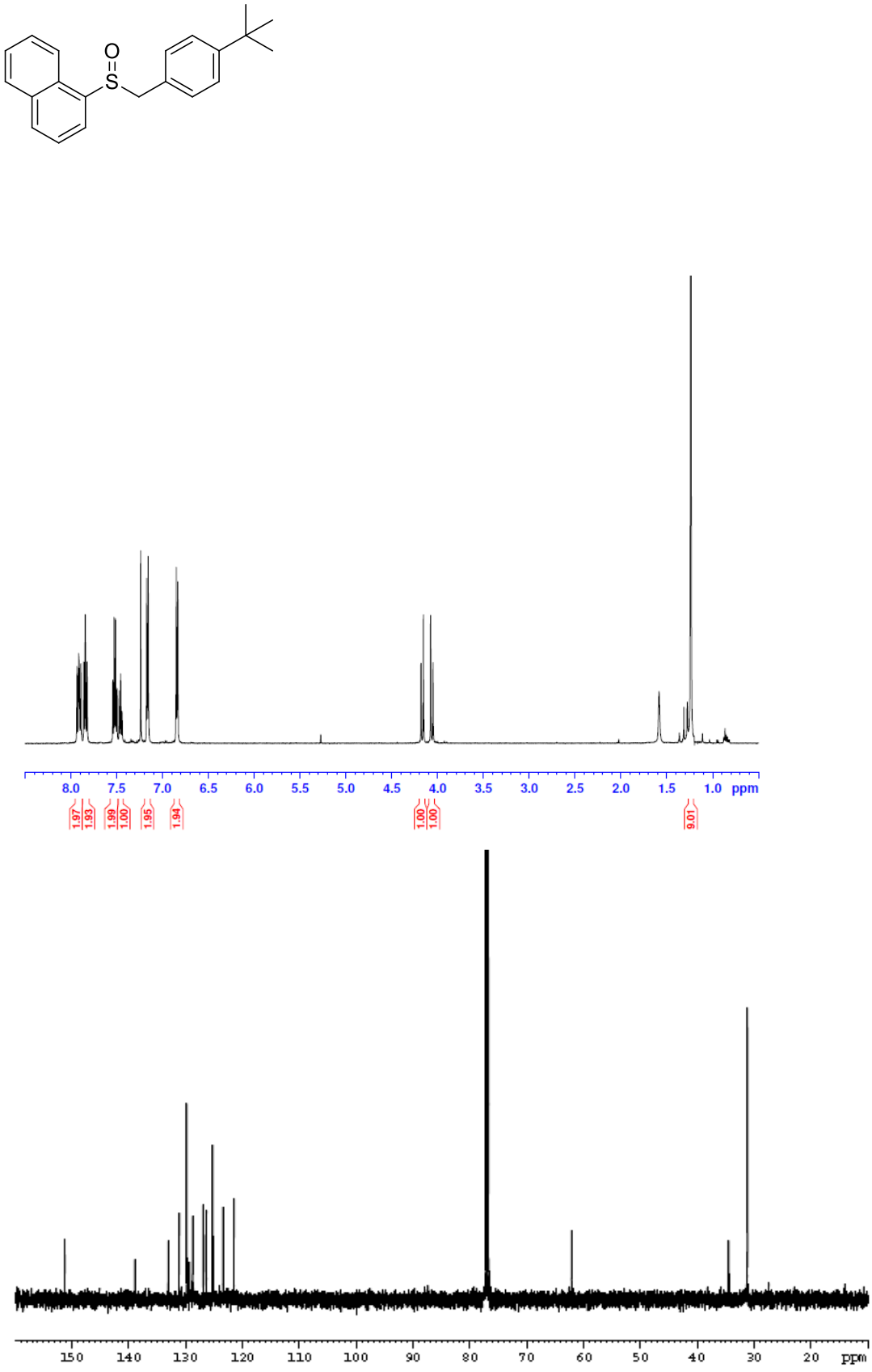


Figure A1.17 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4h** in $CDCl_3$

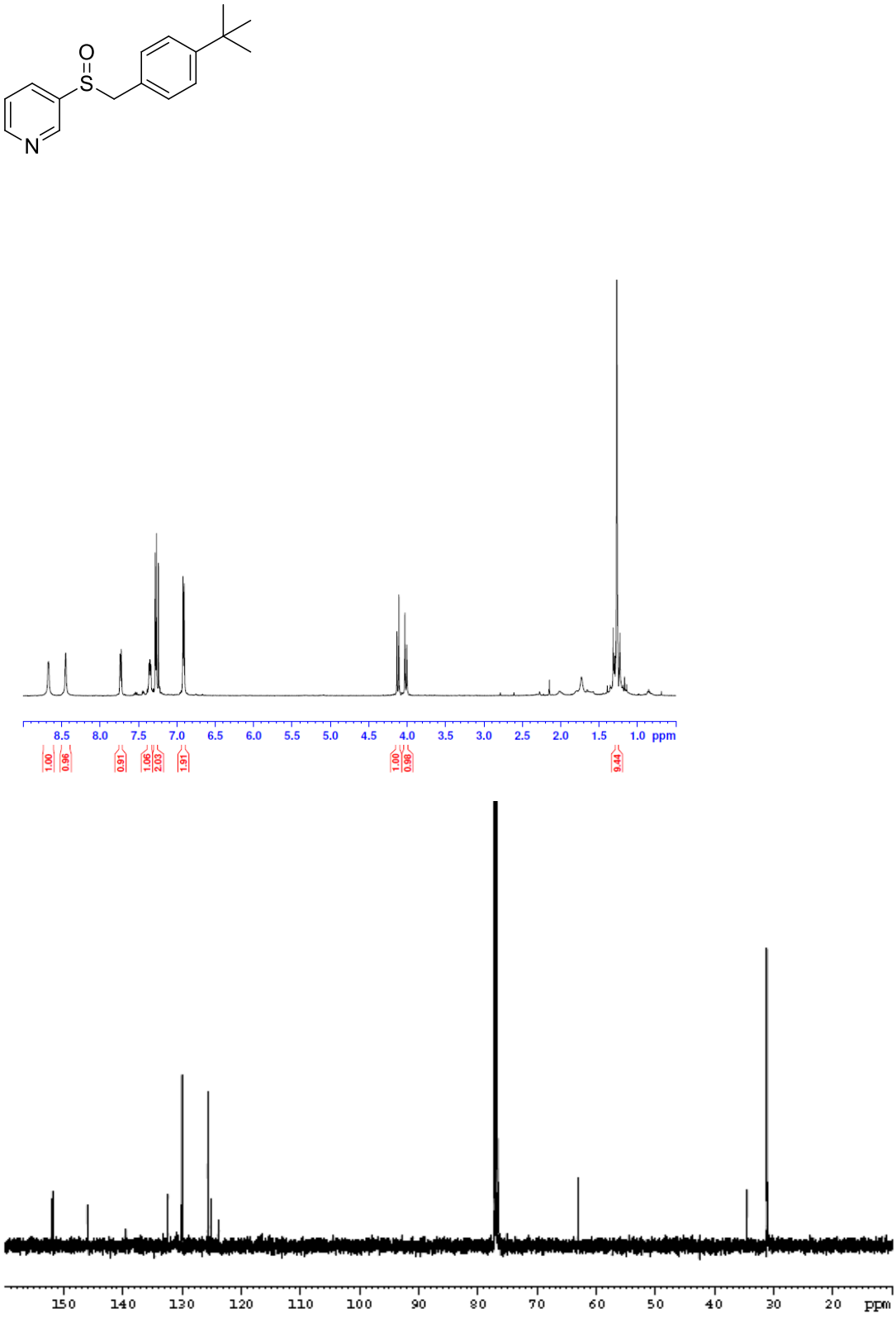


Figure A1.18 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4i** in $CDCl_3$

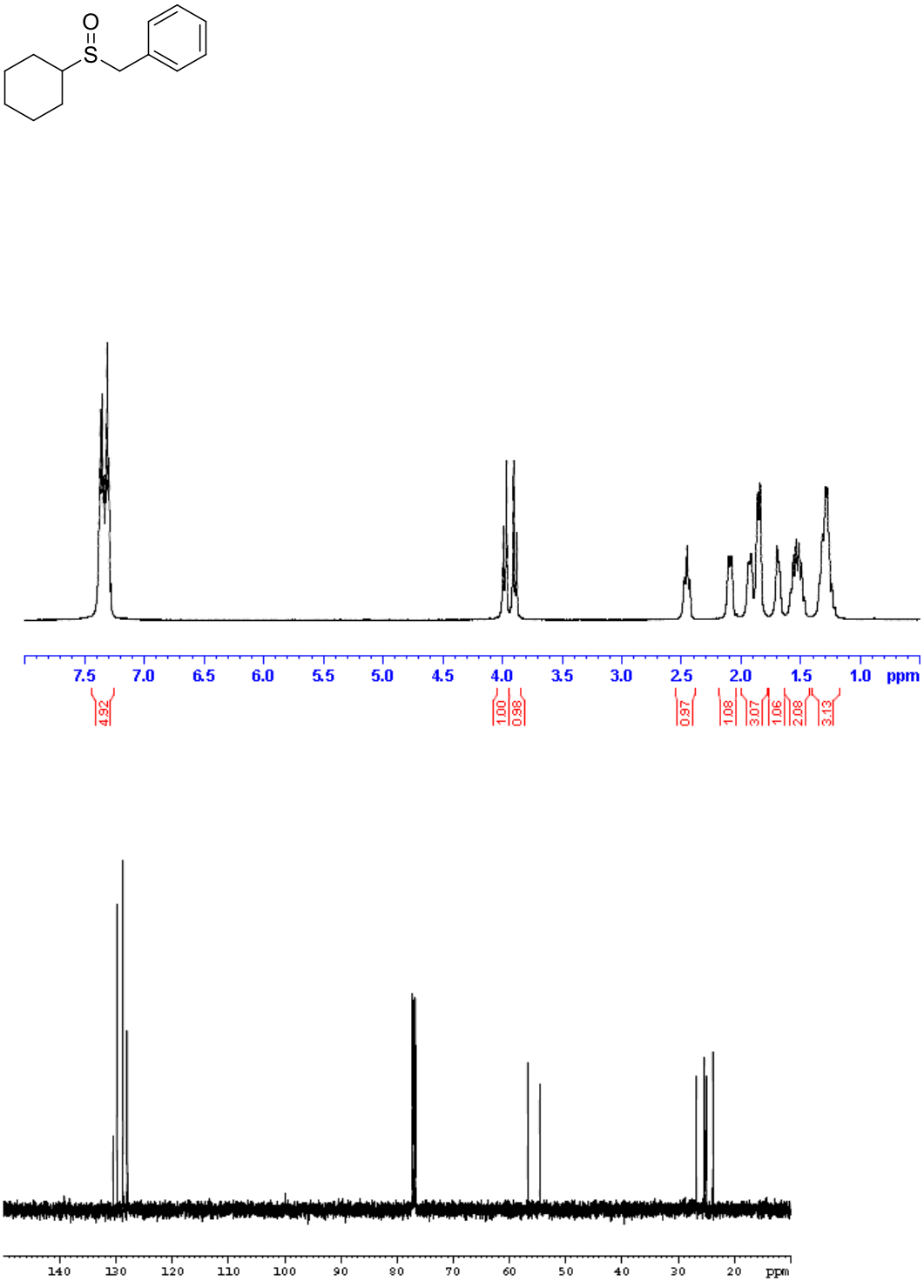
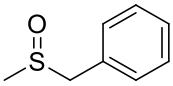
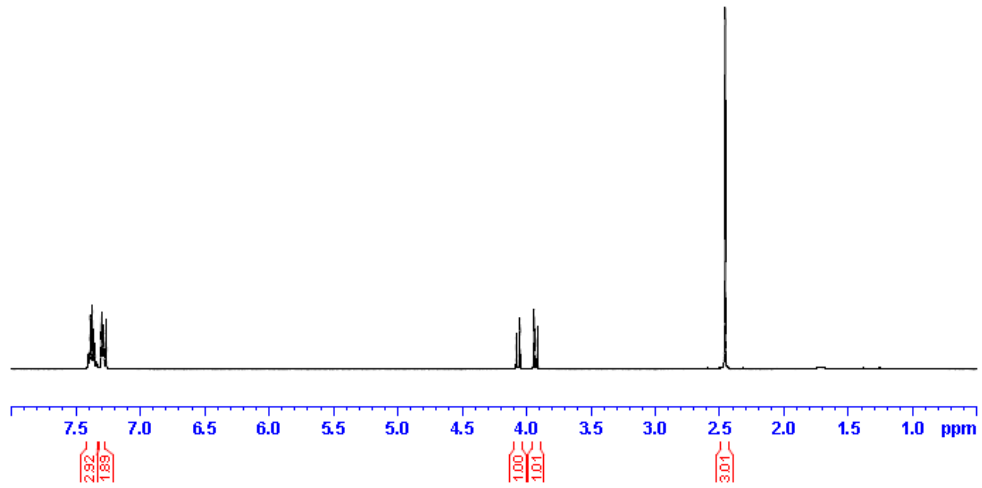


Figure A1.19 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4k** in $CDCl_3$





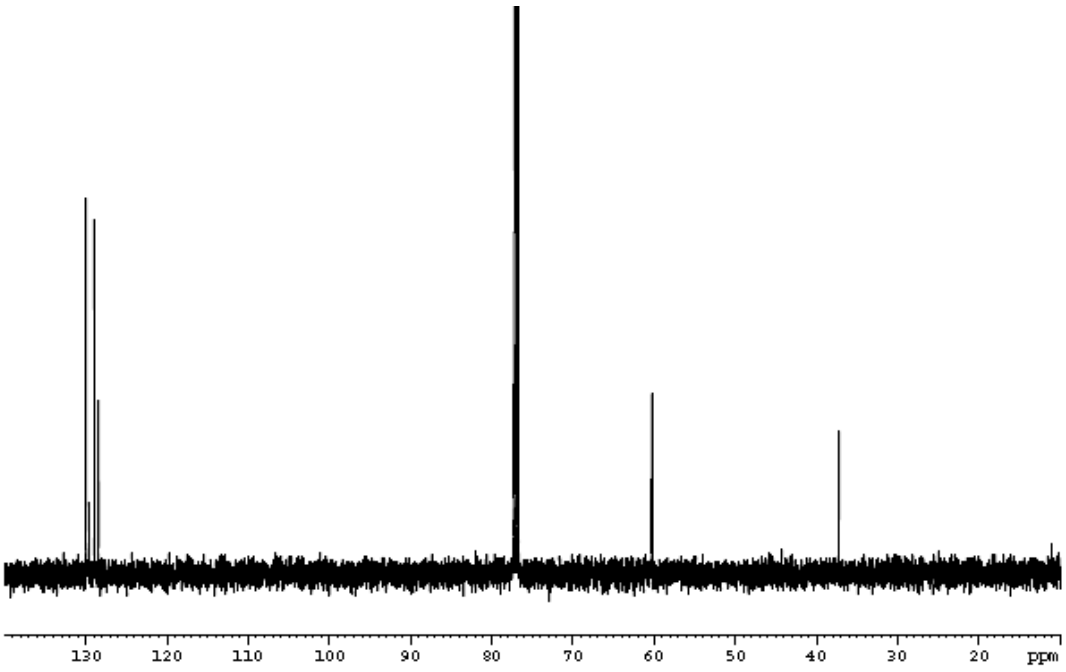
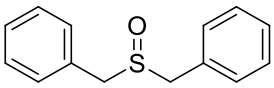
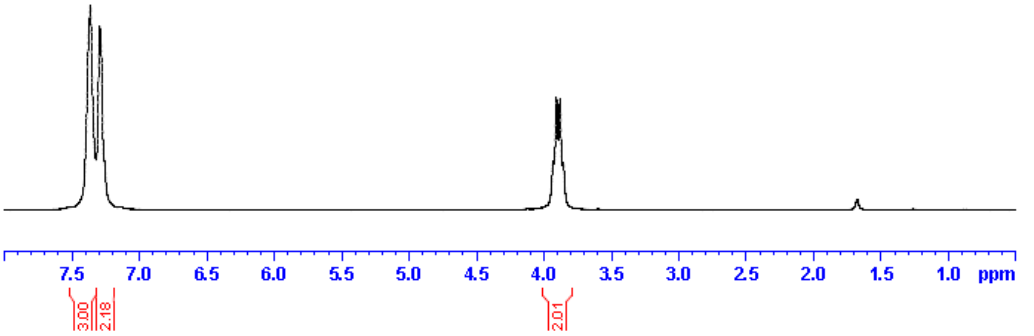


Figure A1.20 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4l** in $CDCl_3$





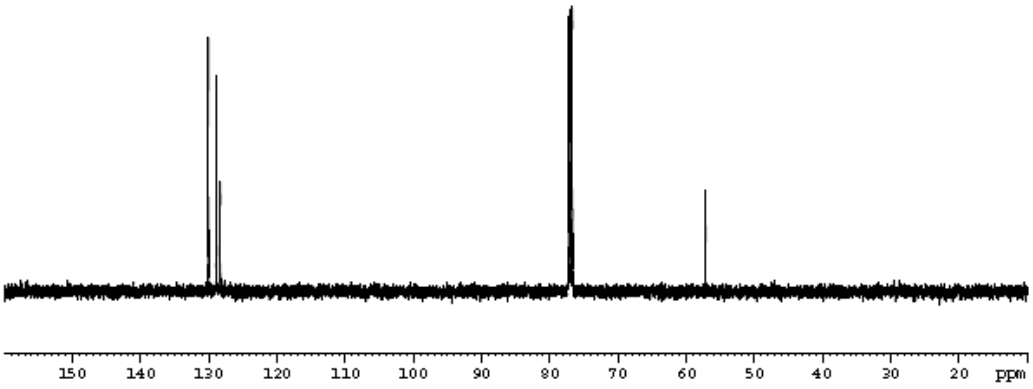
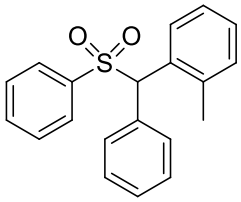
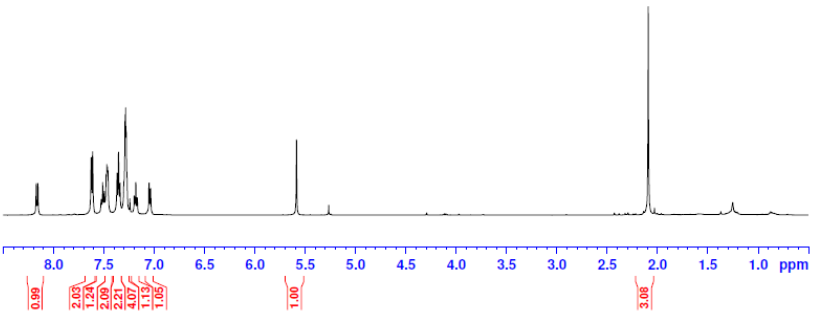


Figure A1.21 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.4l'** in $CDCl_3$





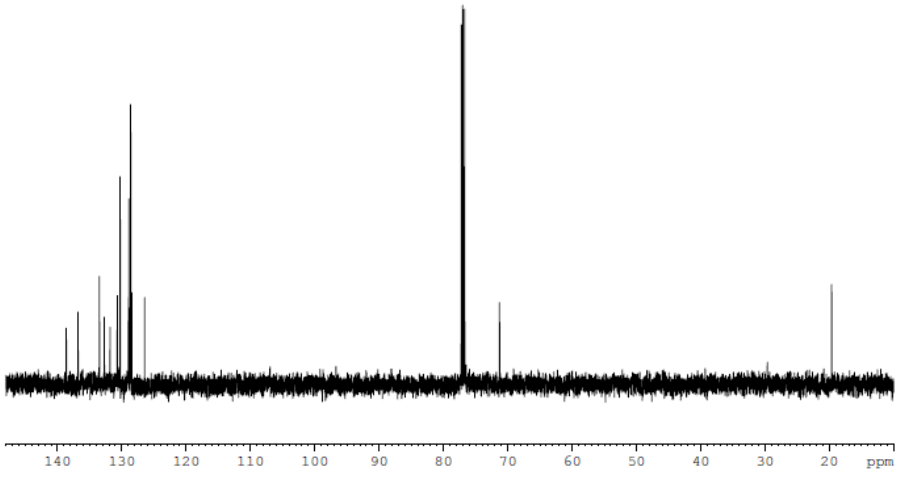


Figure A1.22 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **1.5j** in $CDCl_3$

Appendix A2. NMR Spectra Relevant to Chapter 2

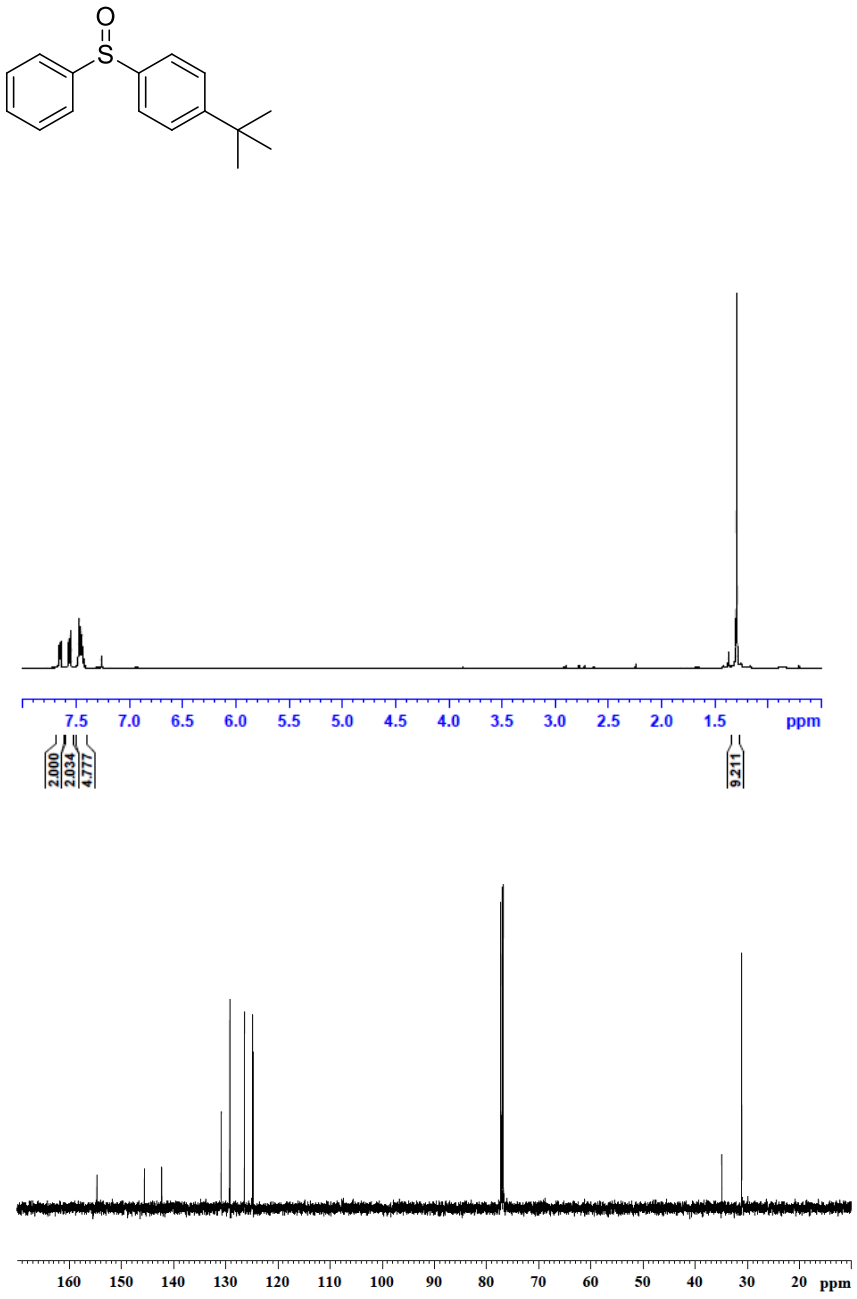


Figure A2.1 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3a** in $CDCl_3$

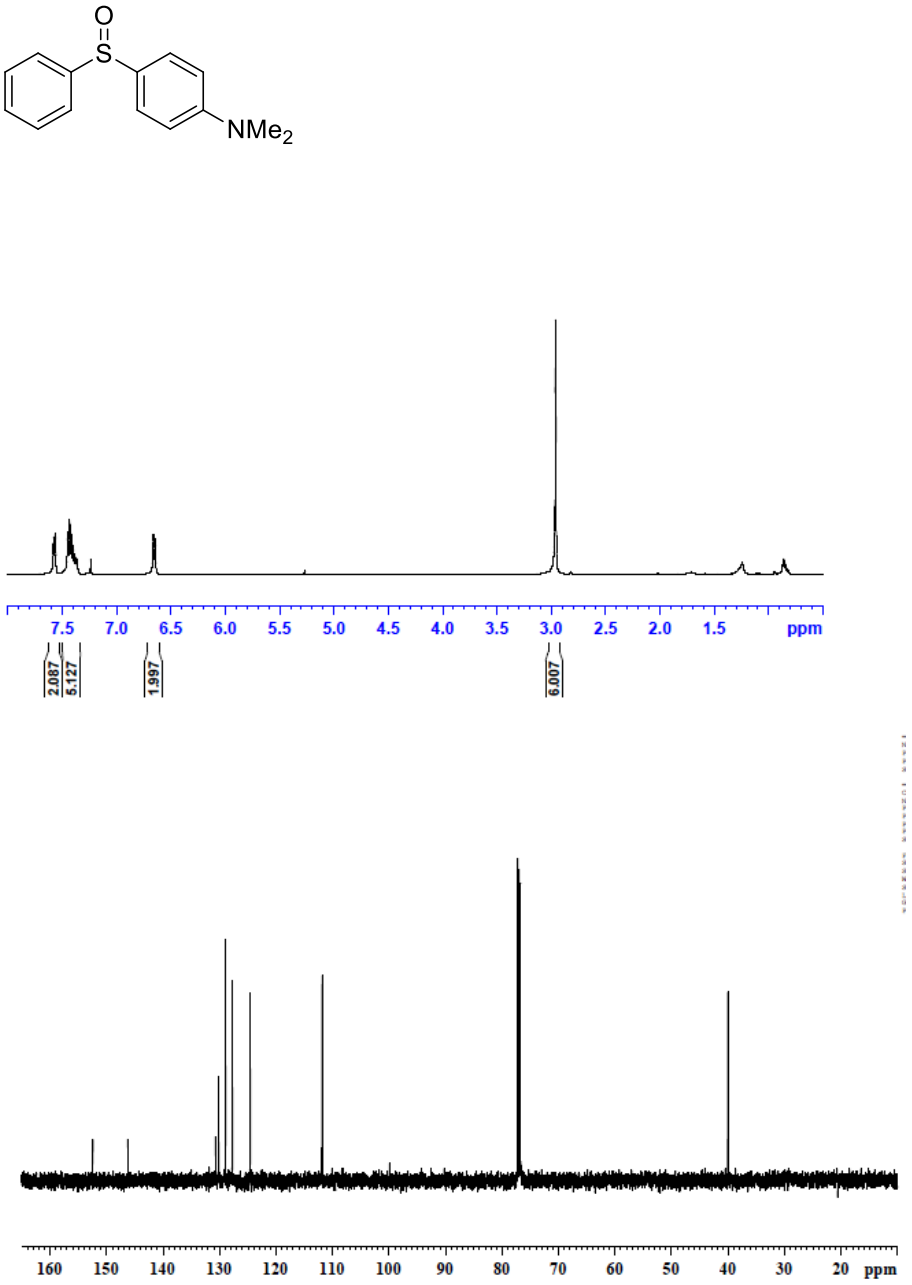
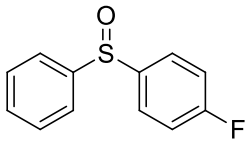
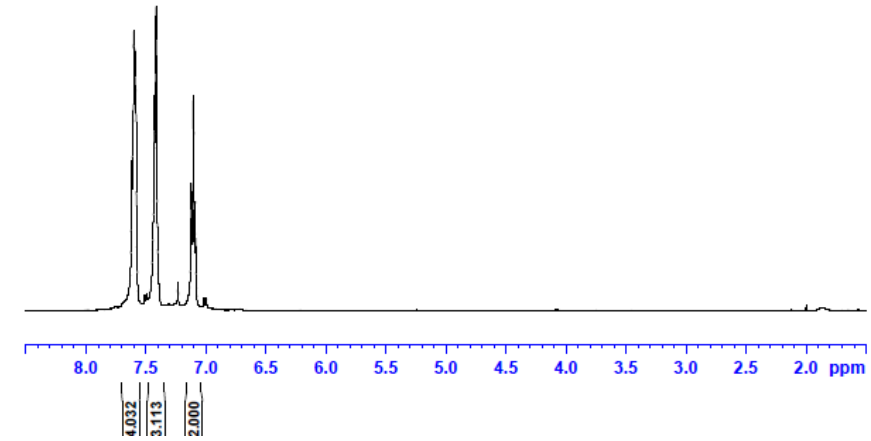


Figure A2.2 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3b** in $CDCl_3$





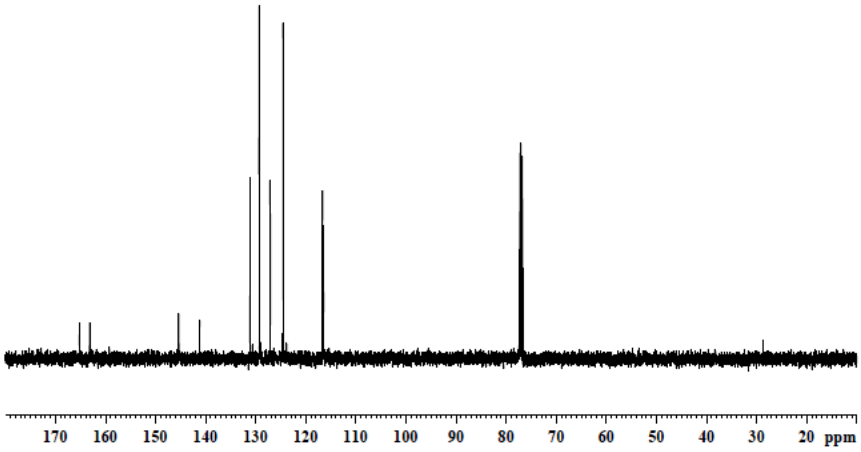


Figure A2.3 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3c** in $CDCl_3$

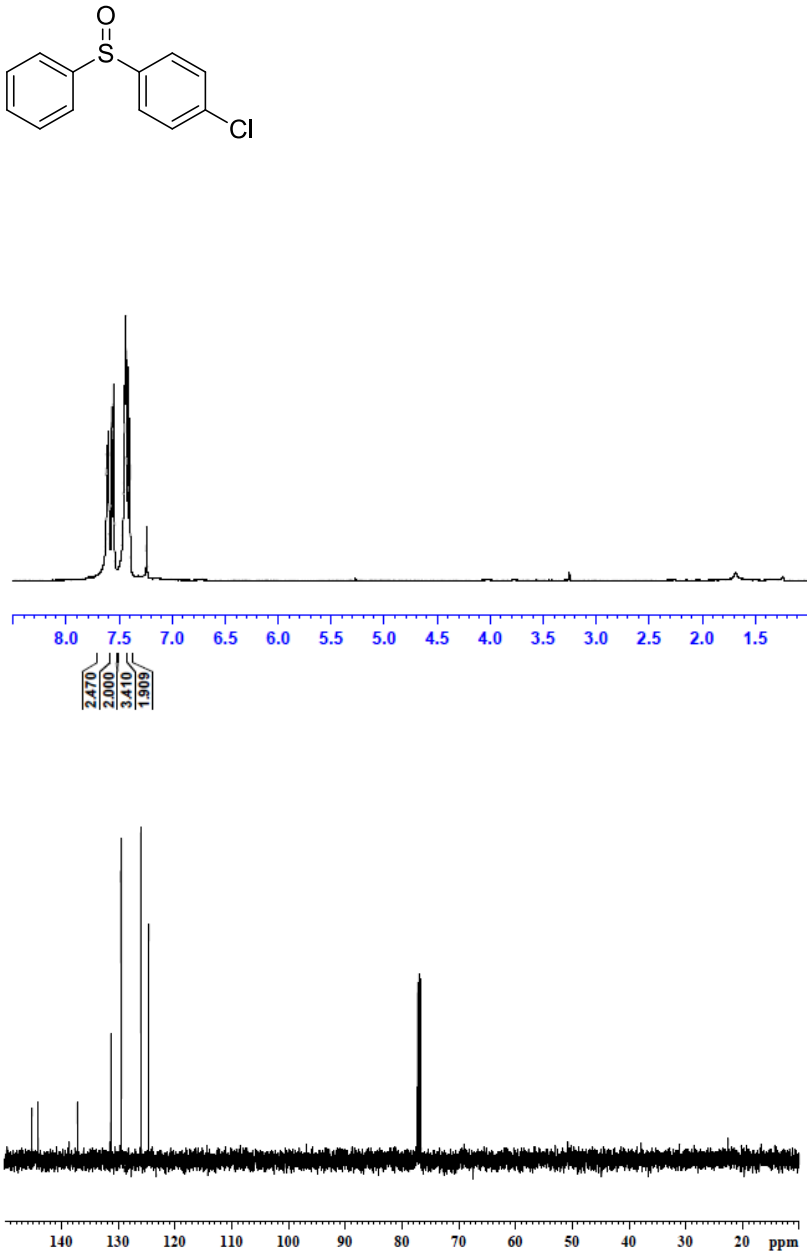


Figure A2.4 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3d** in $CDCl_3$

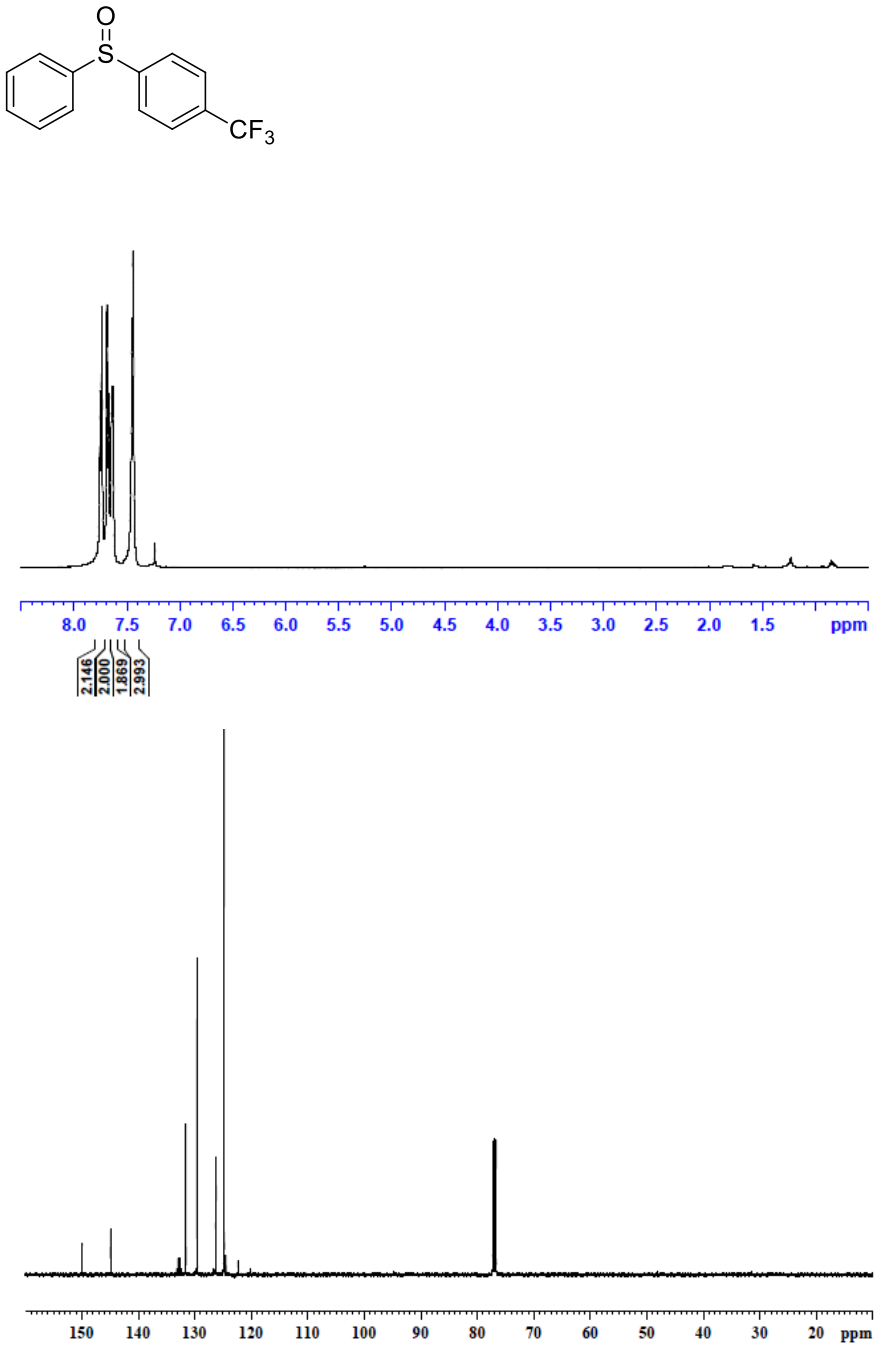


Figure A2.5 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3e** in $CDCl_3$

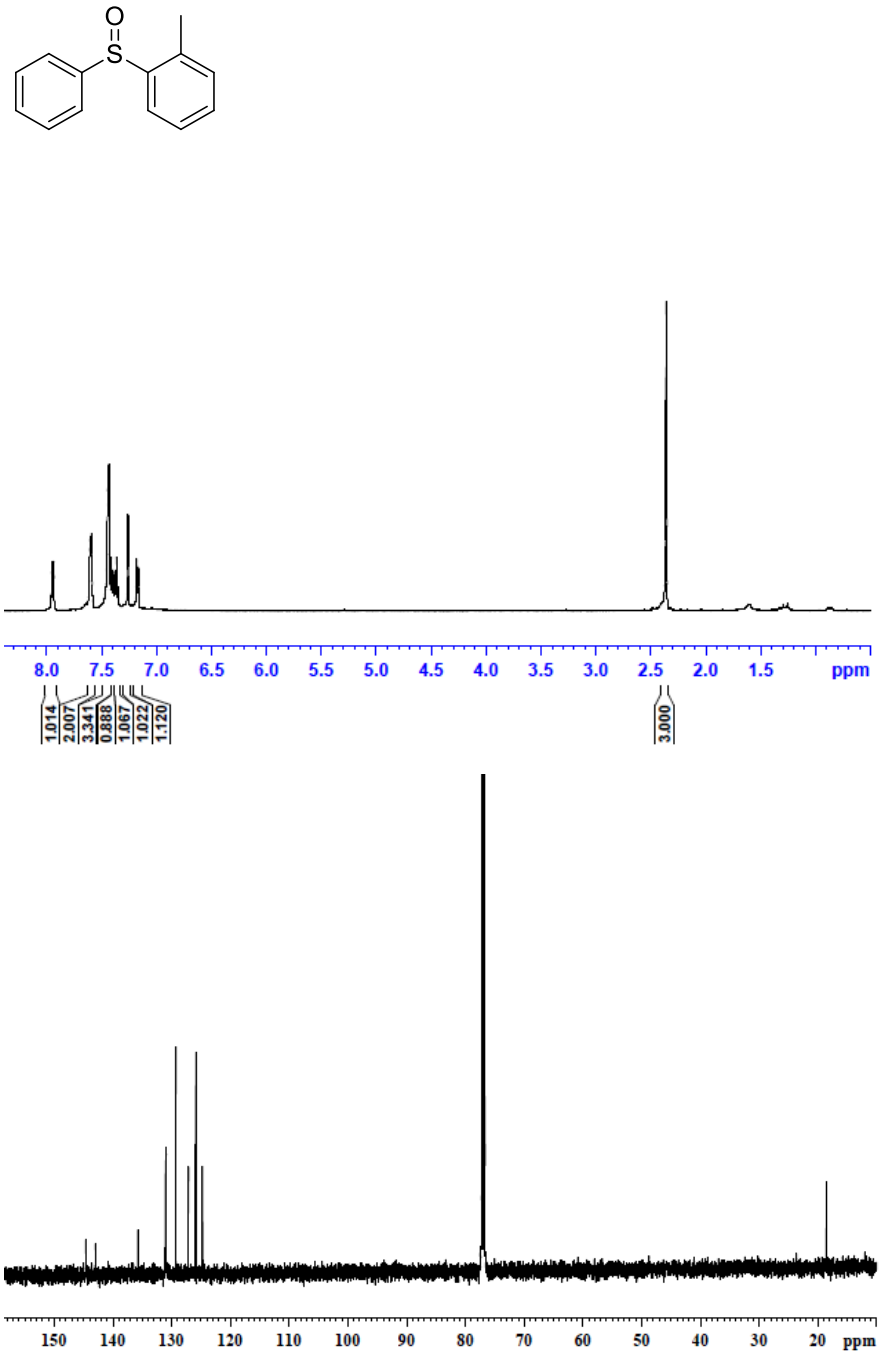


Figure A2.6 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3g** in $CDCl_3$

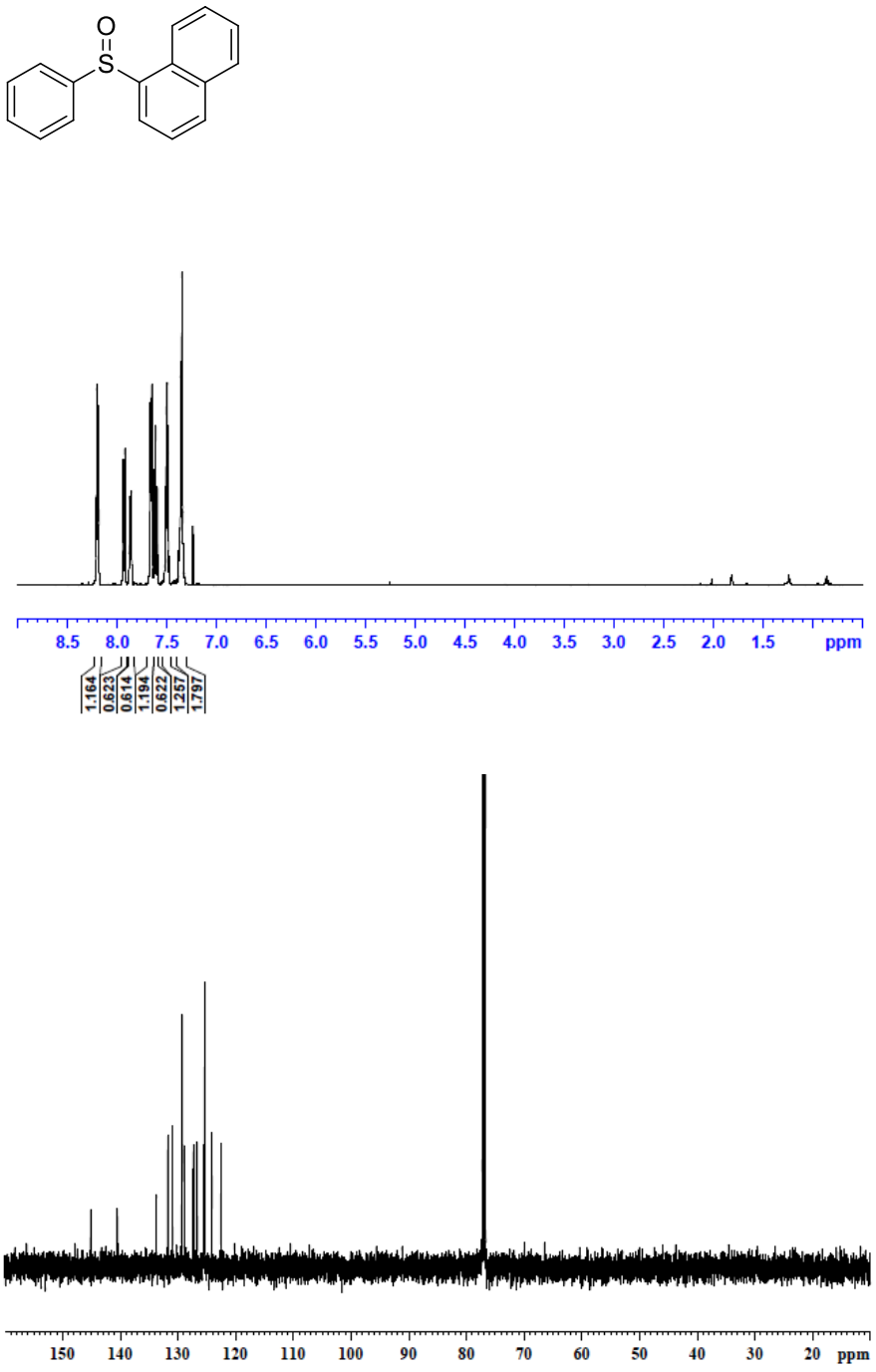


Figure A2.7 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3h** in $CDCl_3$

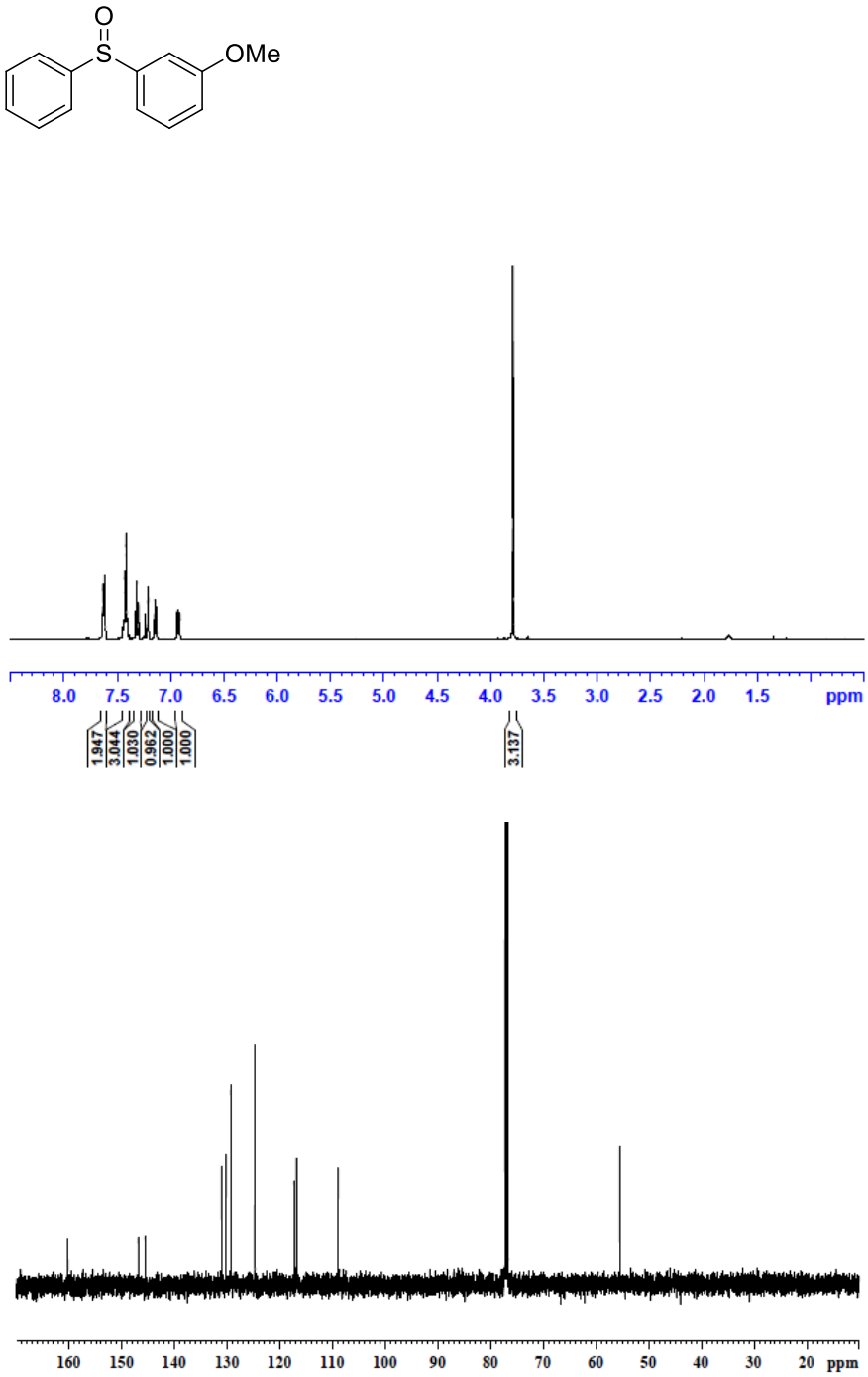


Figure A2.8 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3i** in $CDCl_3$

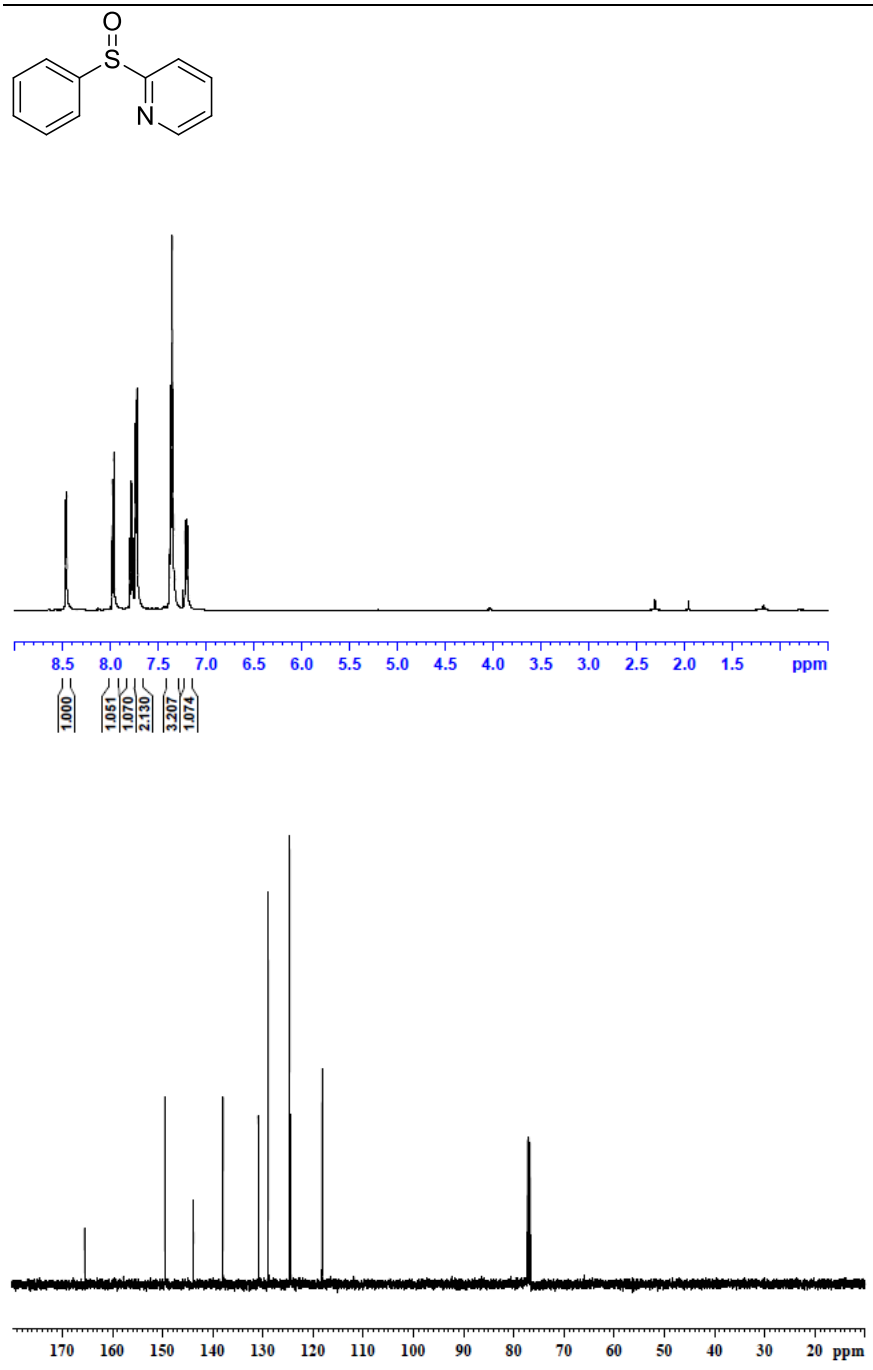


Figure A2.9 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3j** in $CDCl_3$

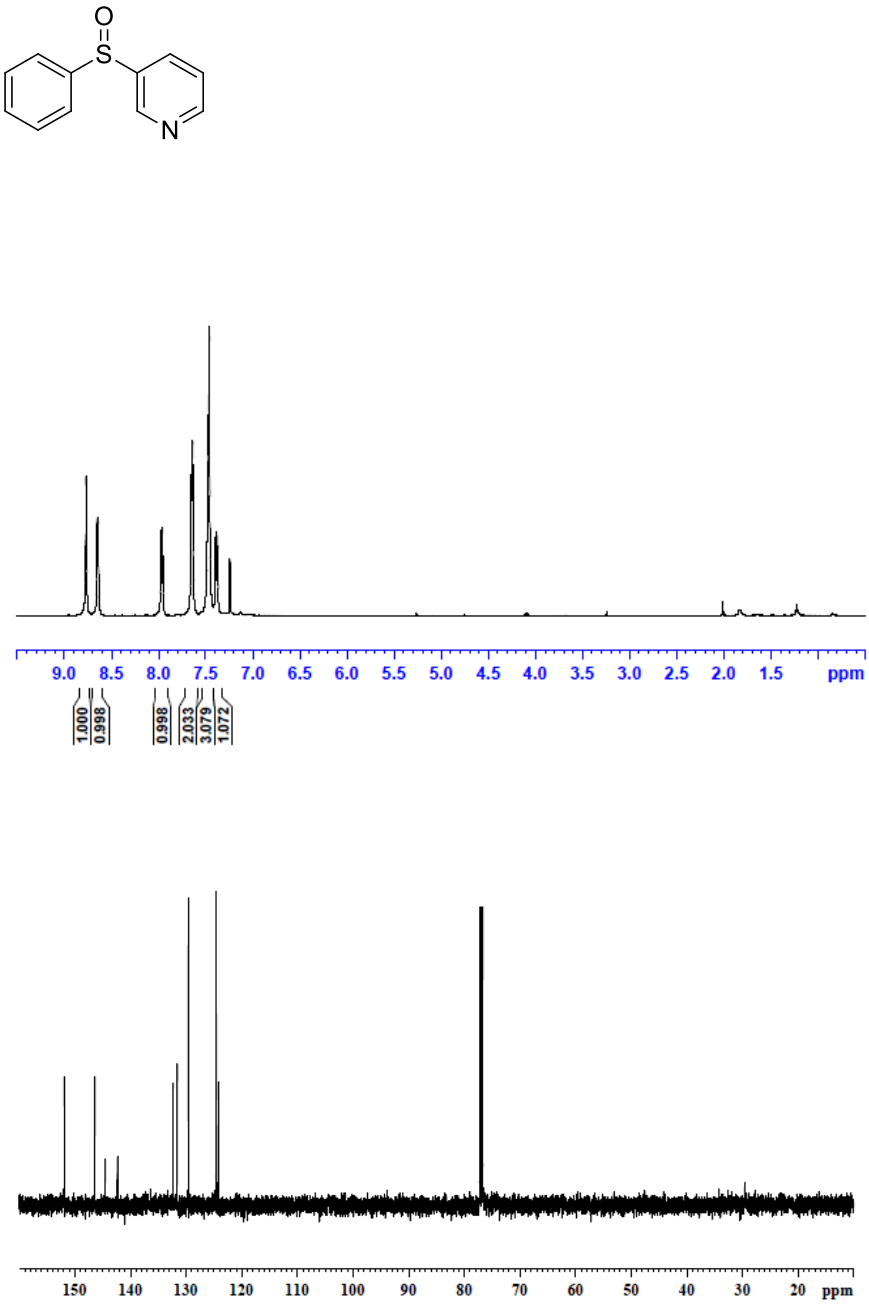


Figure A2.10 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3k** in $CDCl_3$

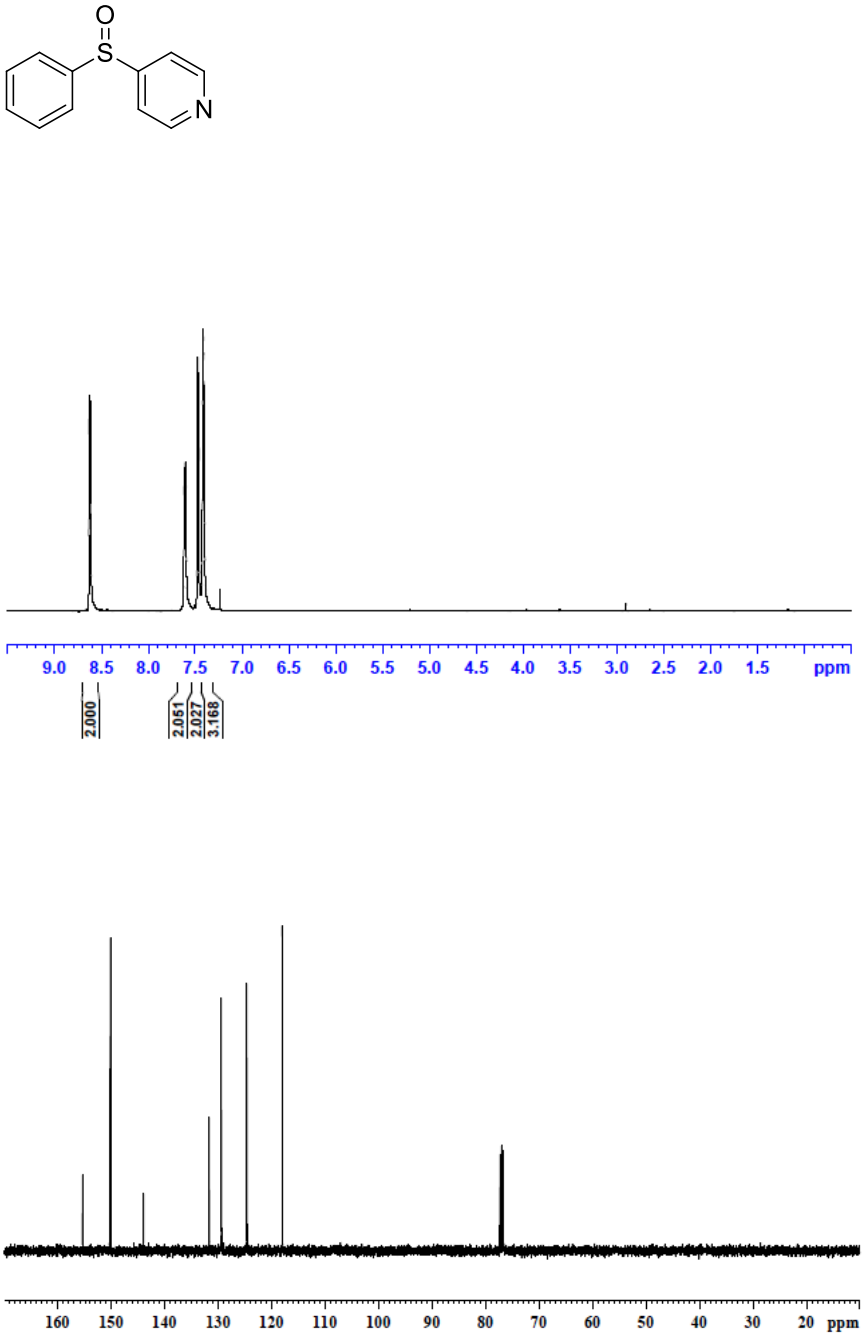


Figure A2.11 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3l** in $CDCl_3$

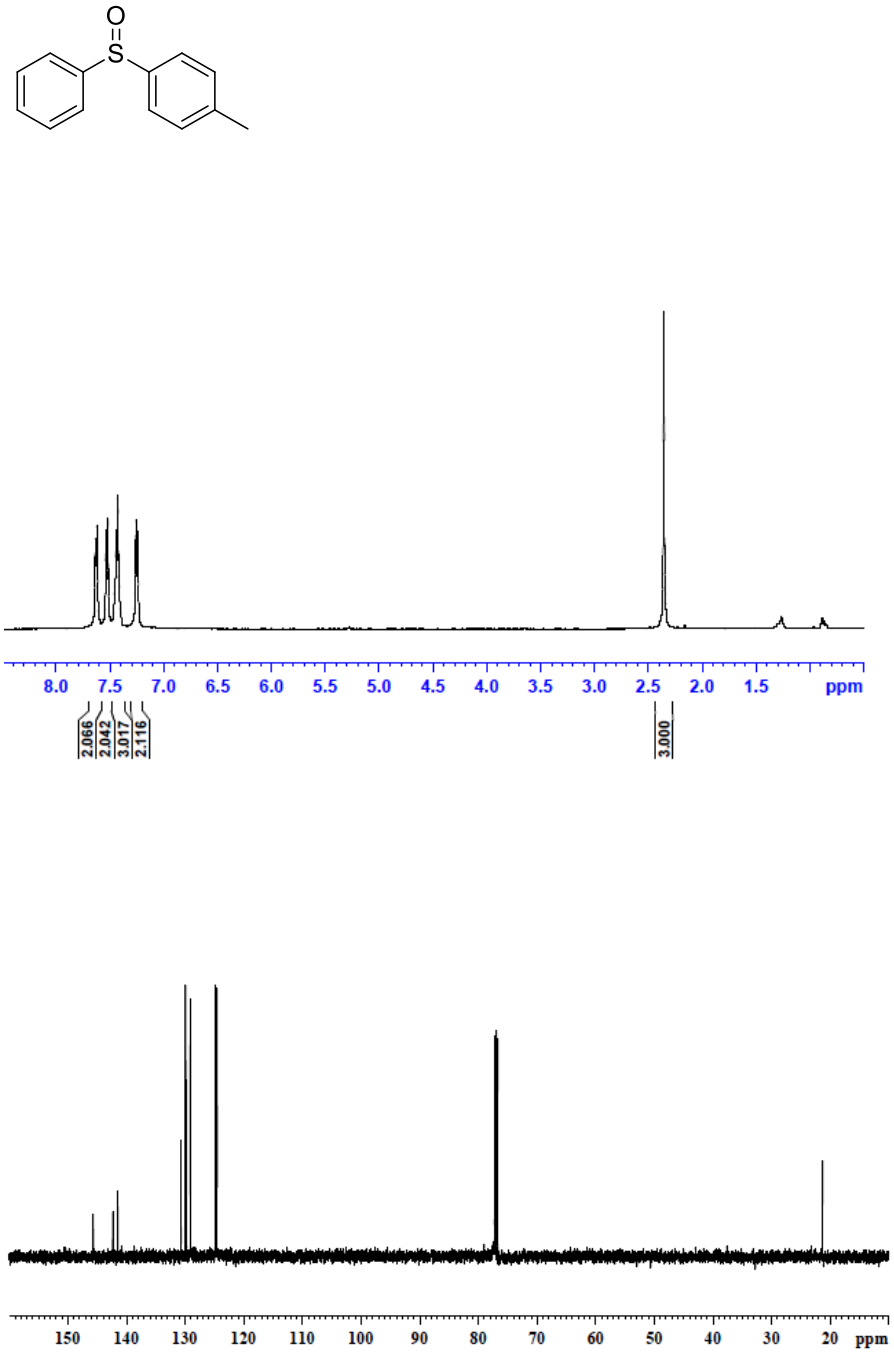


Figure A2.12 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3m** in $CDCl_3$

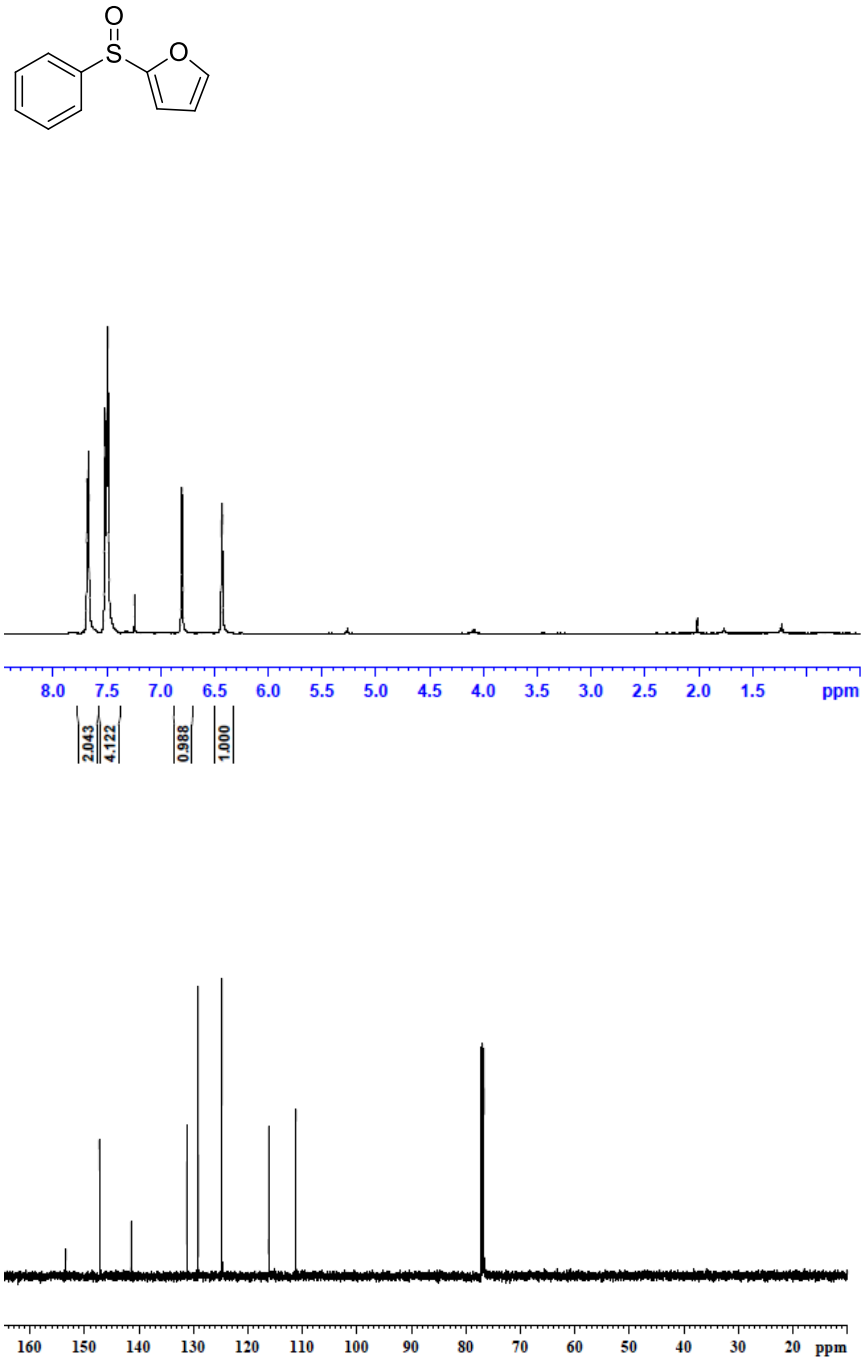


Figure A2.13 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3n** in $CDCl_3$

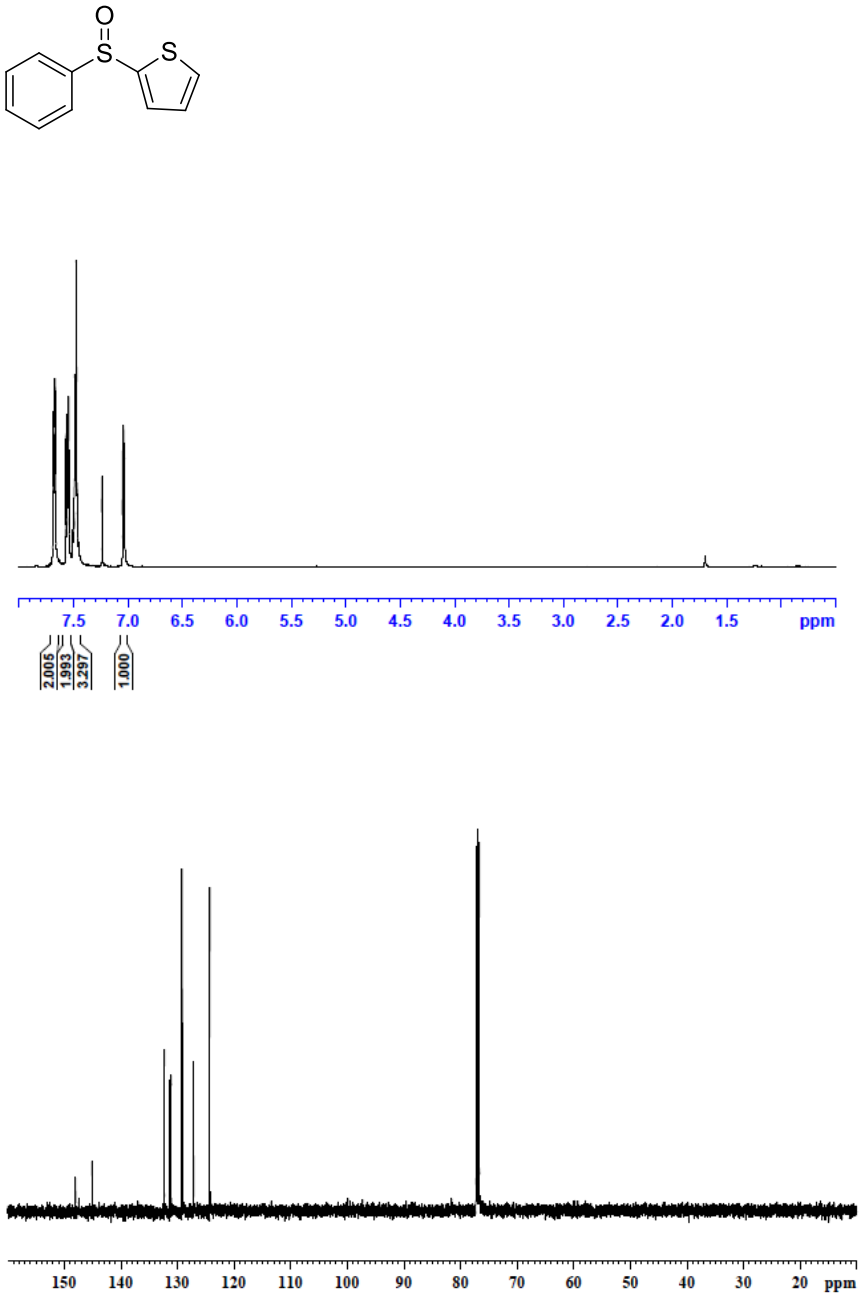


Figure A2.14 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3o** in $CDCl_3$

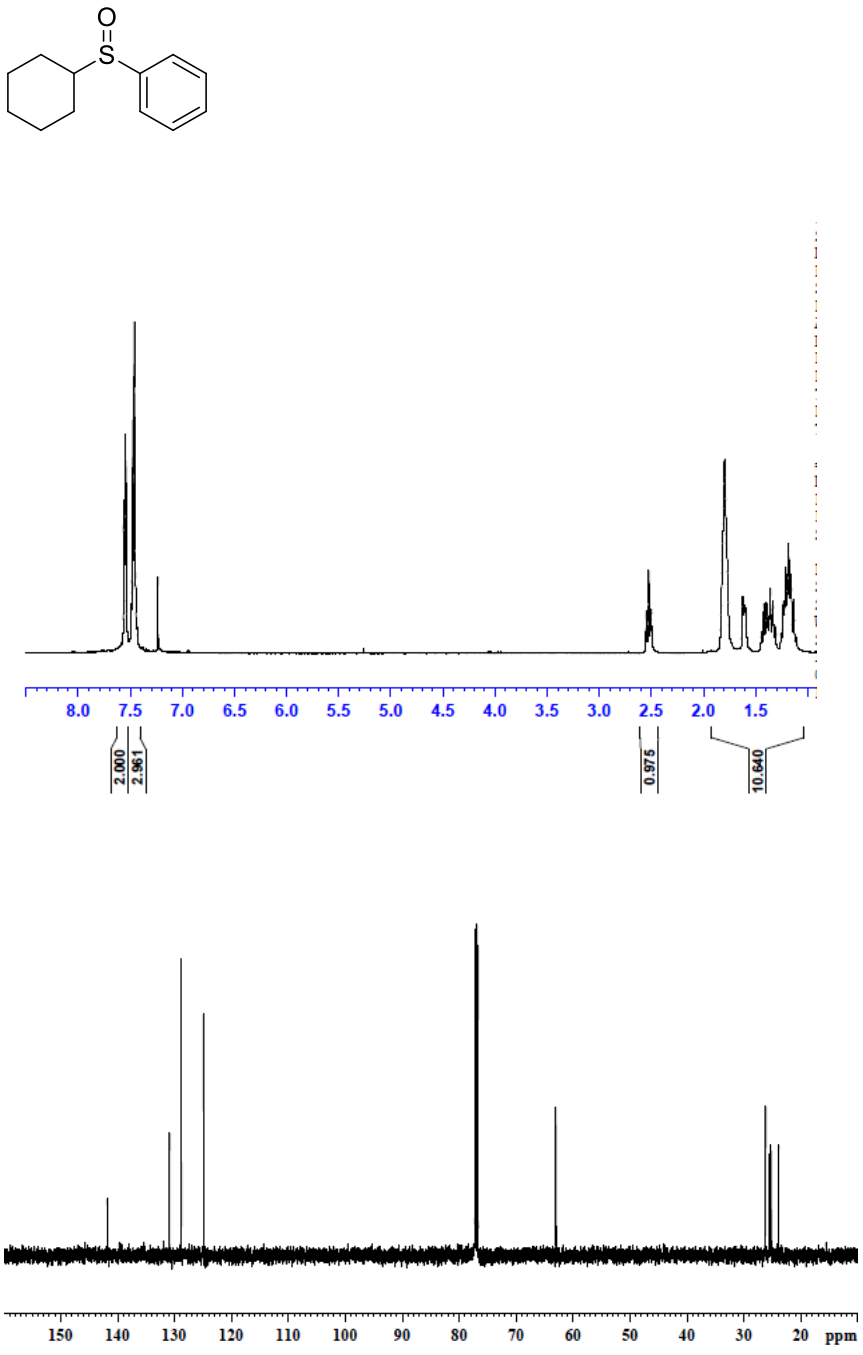


Figure A2.15 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3p** in $CDCl_3$

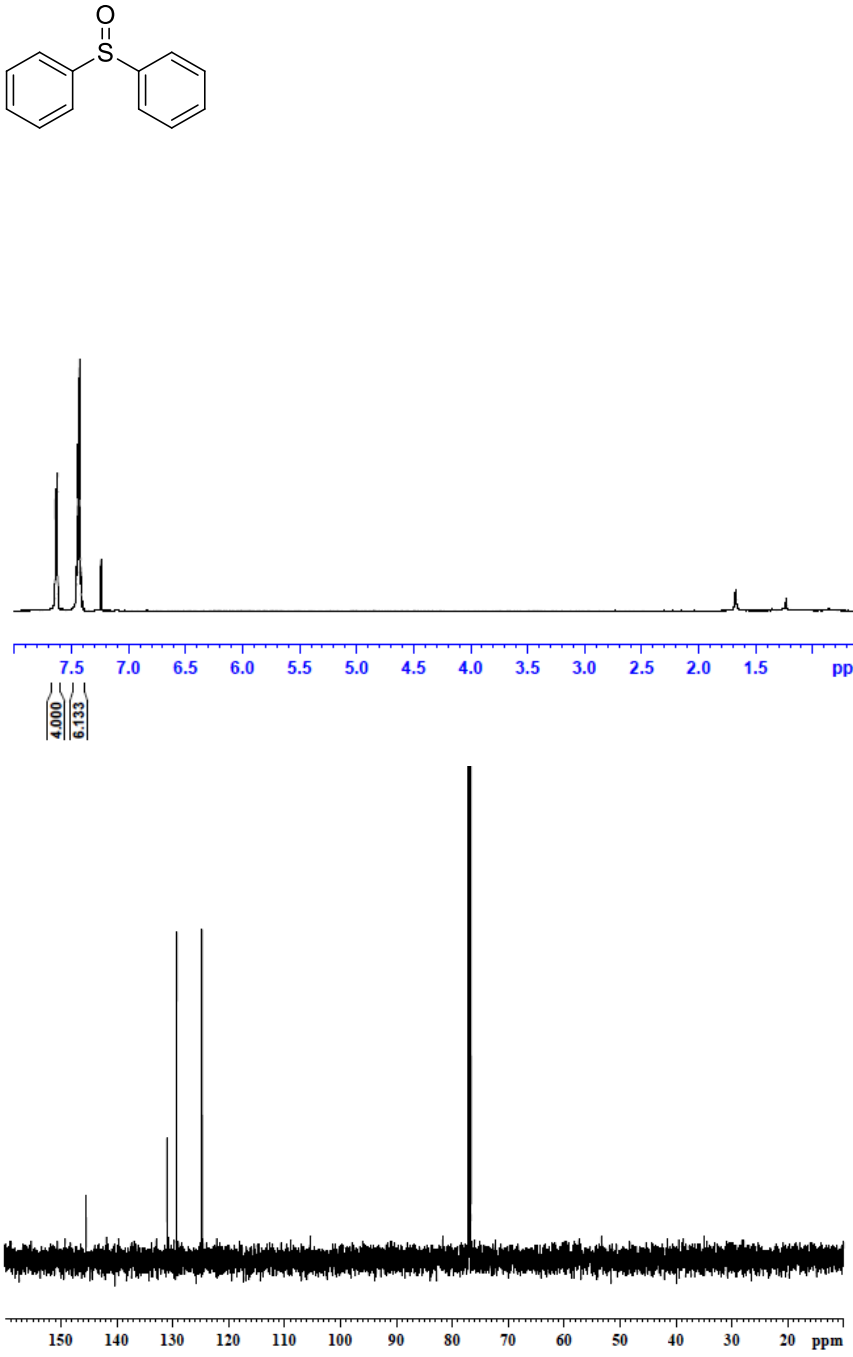


Figure A2.16 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of **2.3q** in $CDCl_3$

Appendix A3. NMR Spectra Relevant to Chapter 3

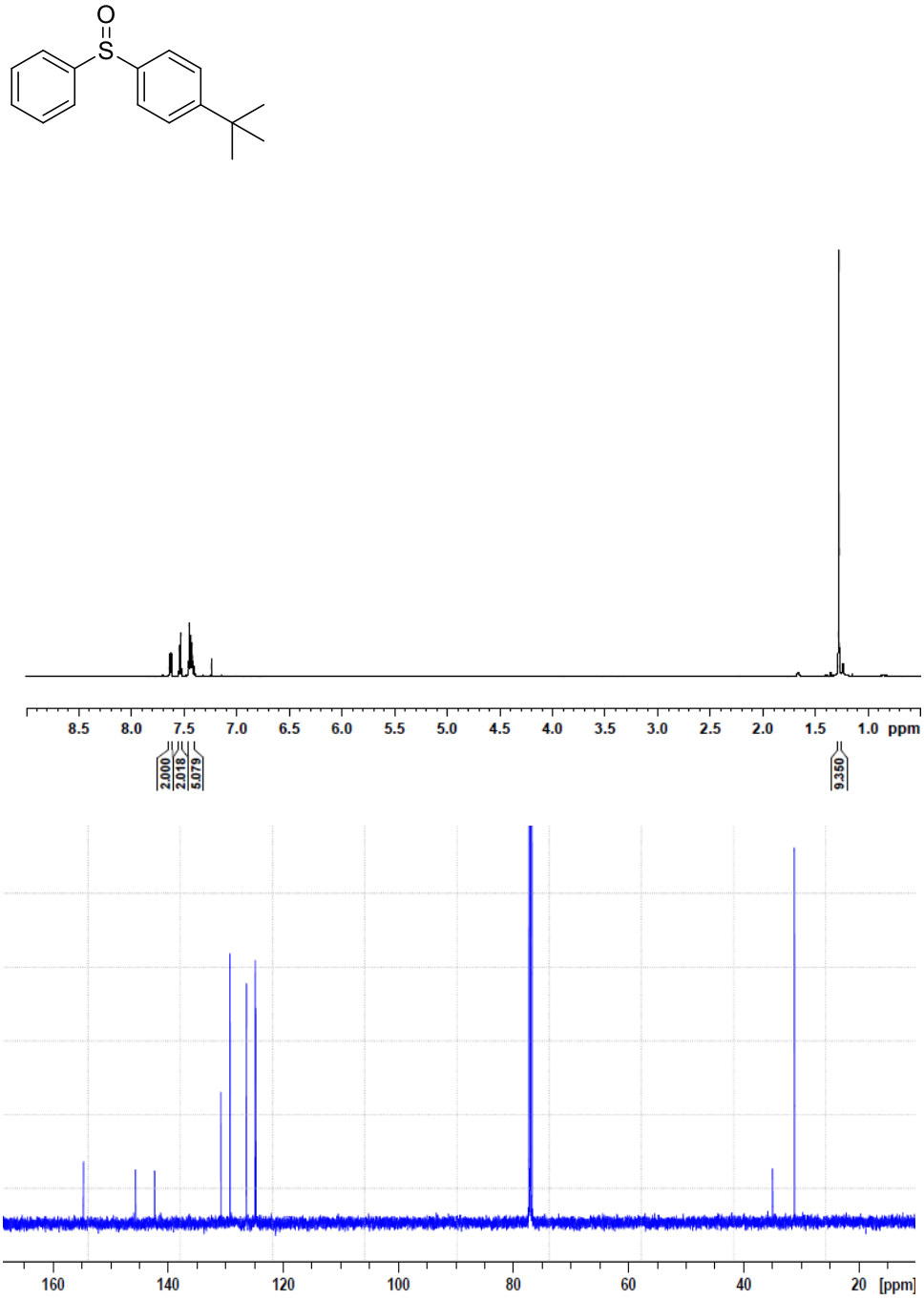


Figure A3.1. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3a** in $CDCl_3$.

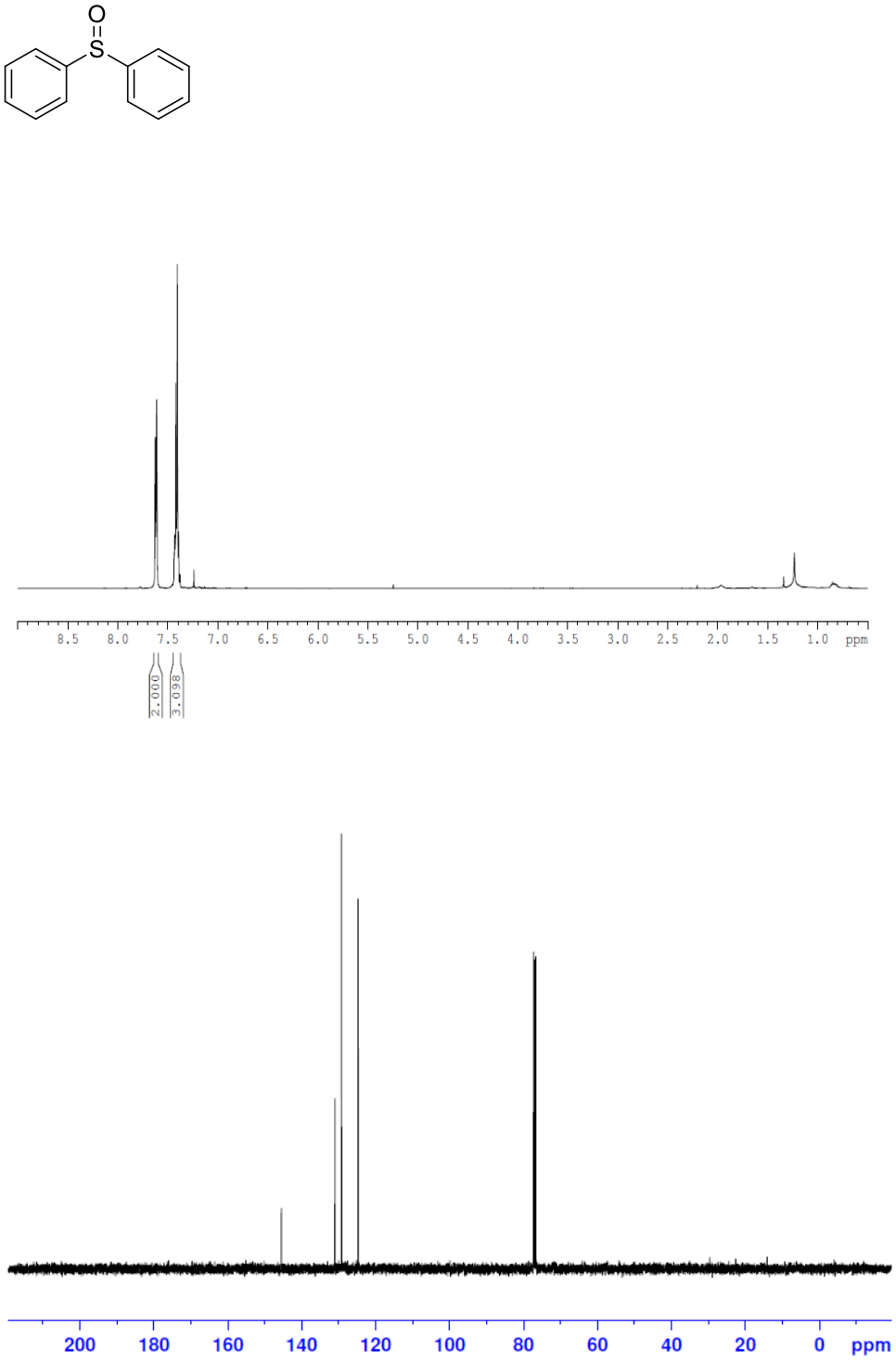


Figure A3.2. ^{1}H (500 MHz) and ^{13}C $\{^{1}H\}$ (125 MHz) NMR spectra of **3.3b** in $CDCl_3$.

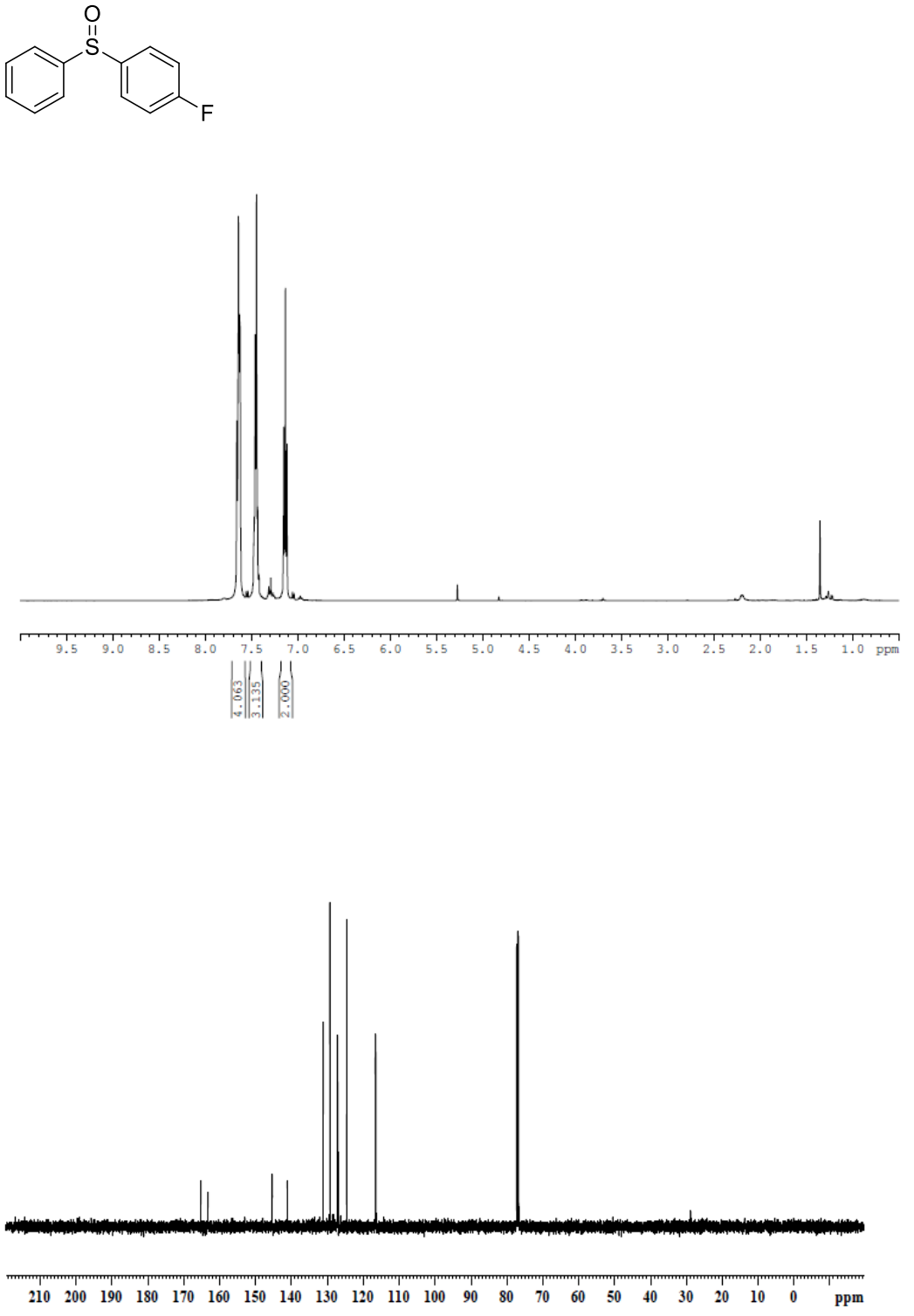


Figure A3.3. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3c** in $CDCl_3$.

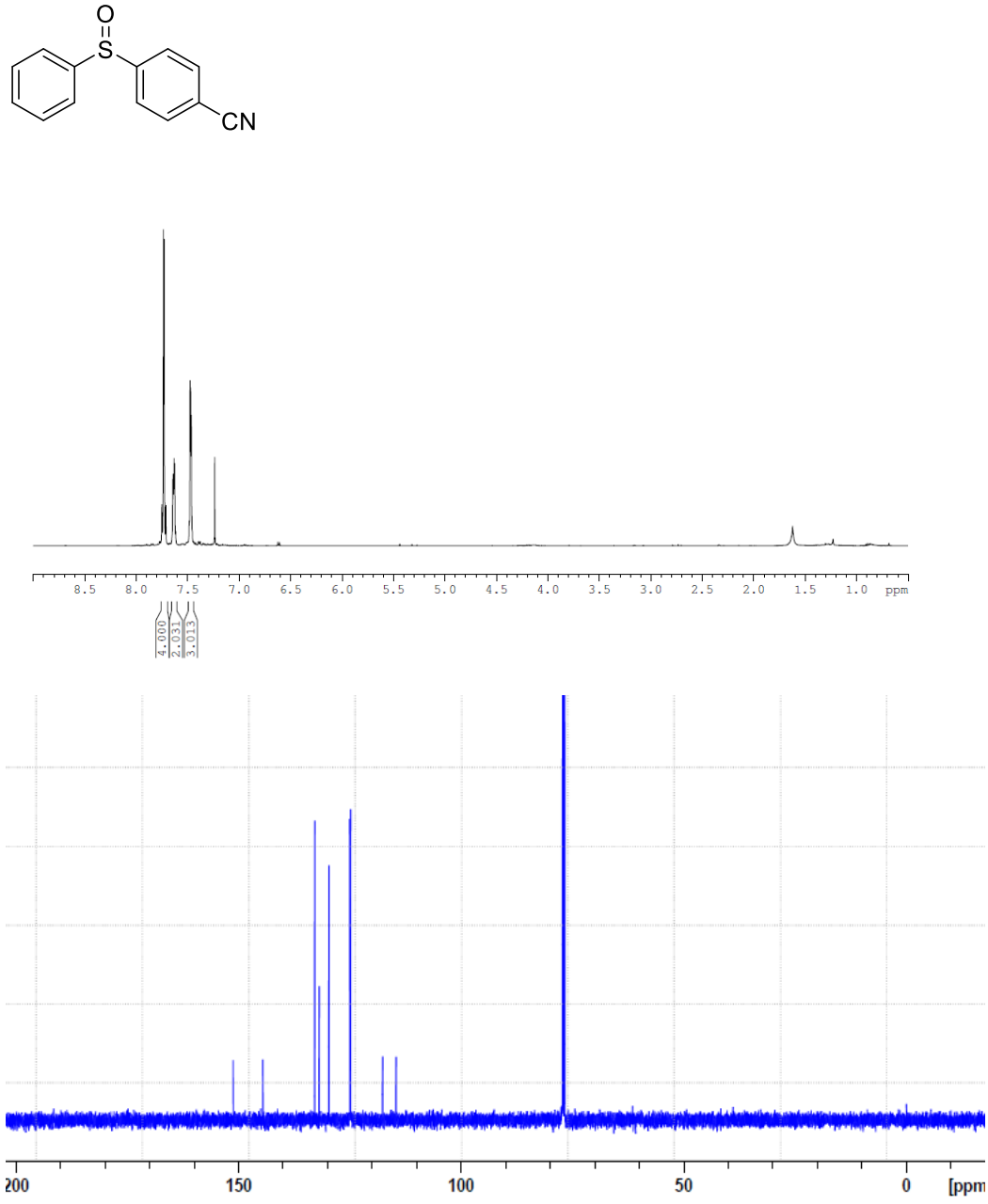


Figure A3.4. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3d** in $CDCl_3$.

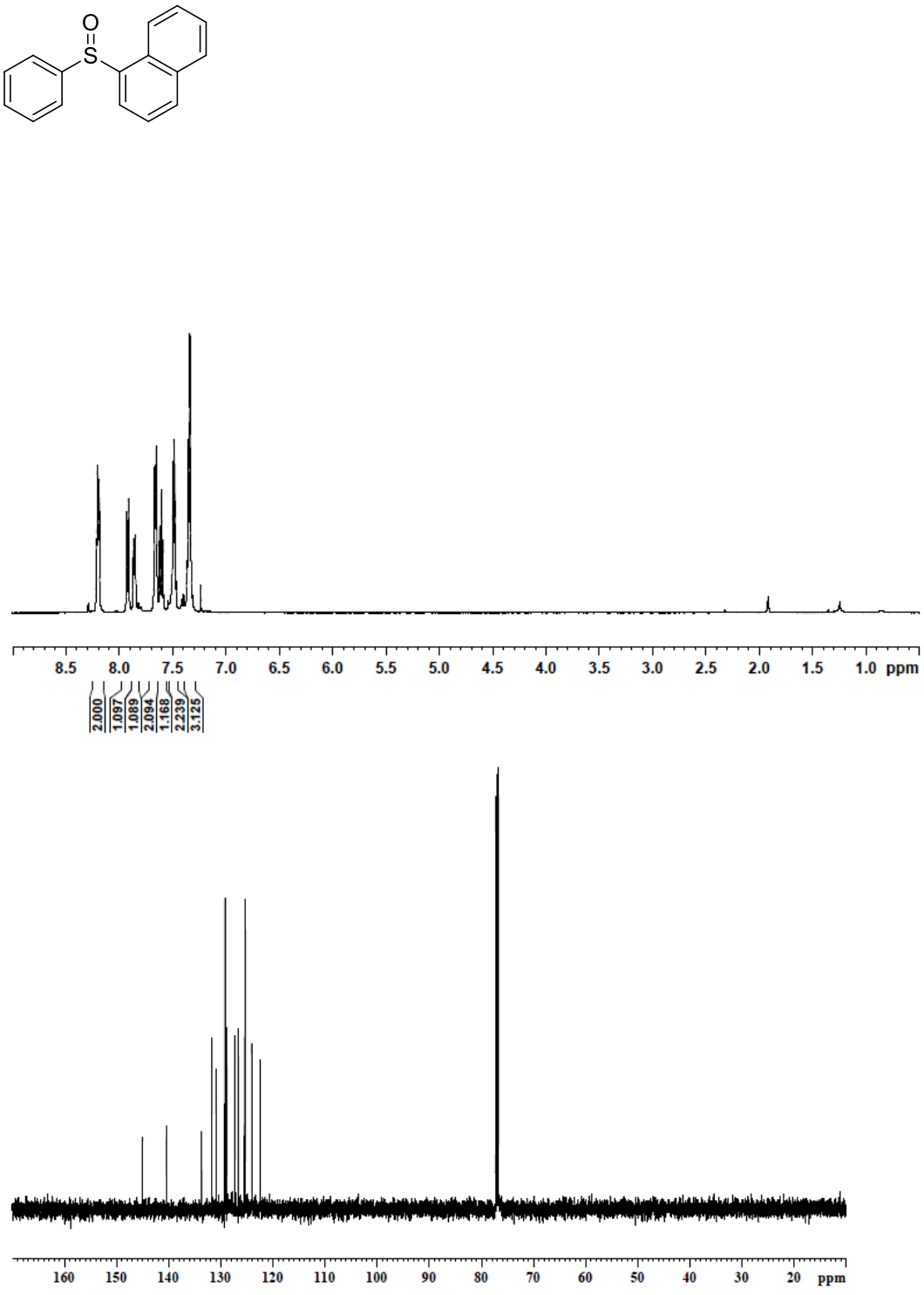


Figure A3.5. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3e** in $CDCl_3$.

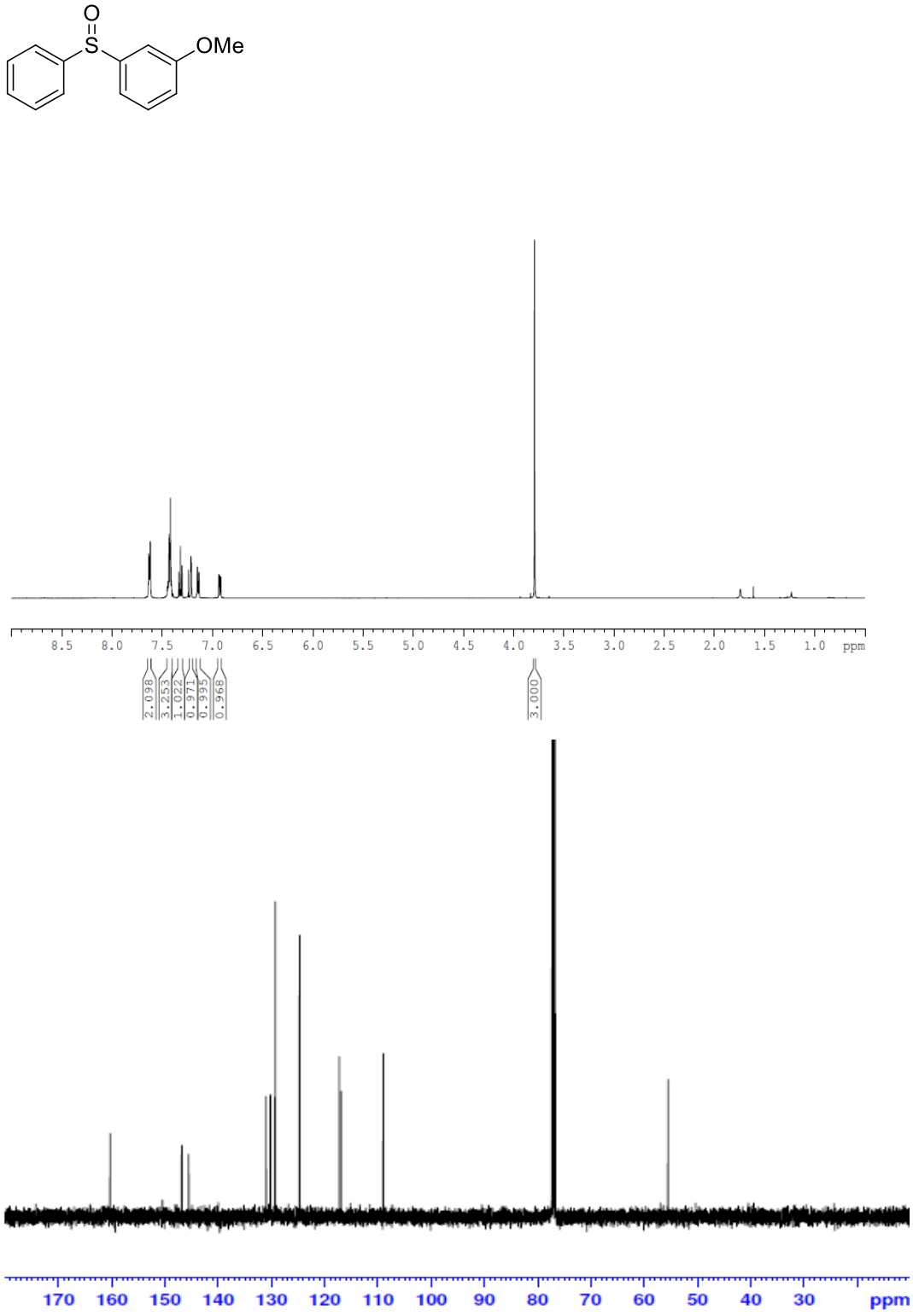


Figure A3.6. ^{1}H (500 MHz) and ^{13}C $\{^{1}H\}$ (125 MHz) NMR spectra of **3.3f** in $CDCl_3$.

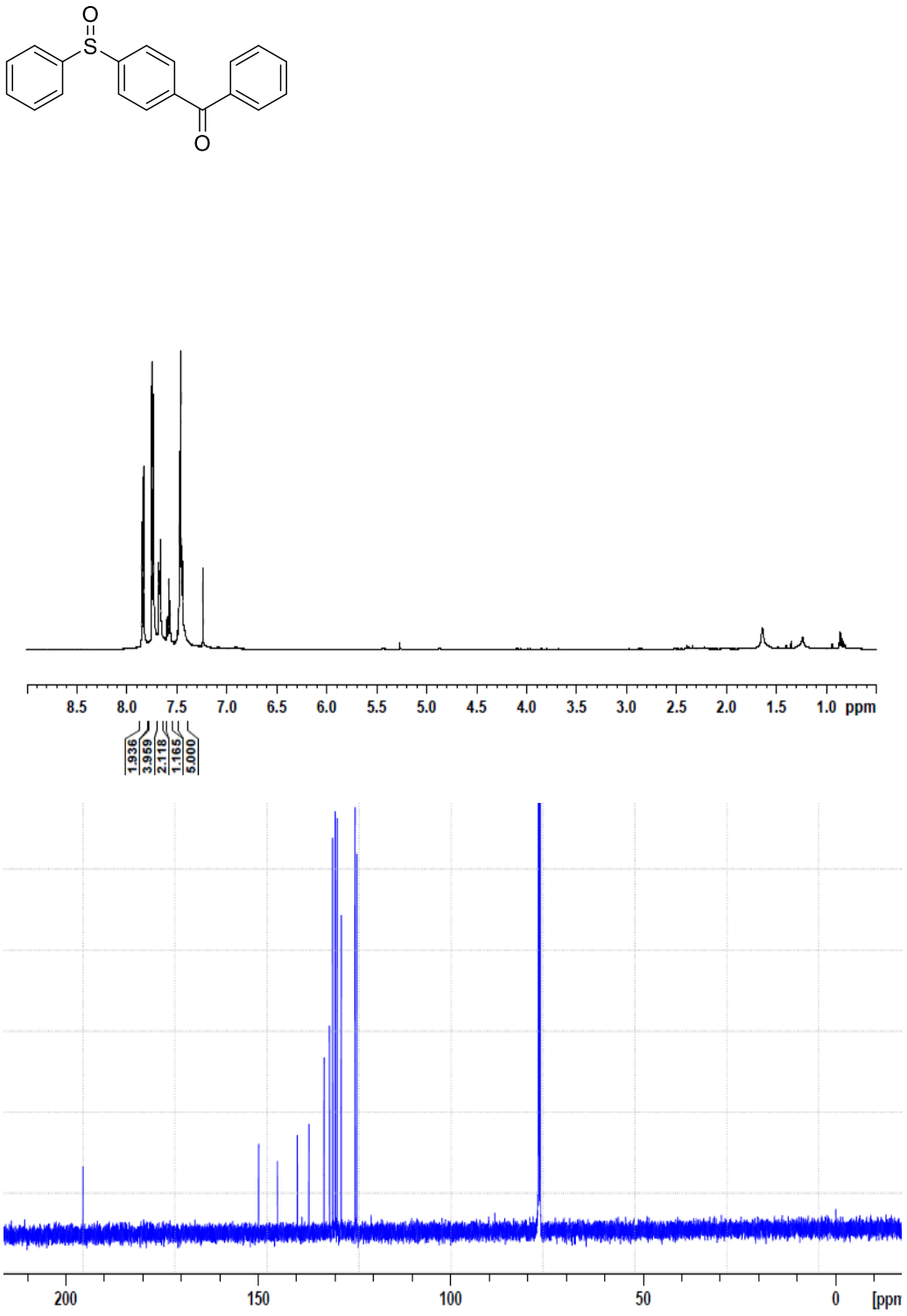


Figure A3.7. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3g** in $CDCl_3$.

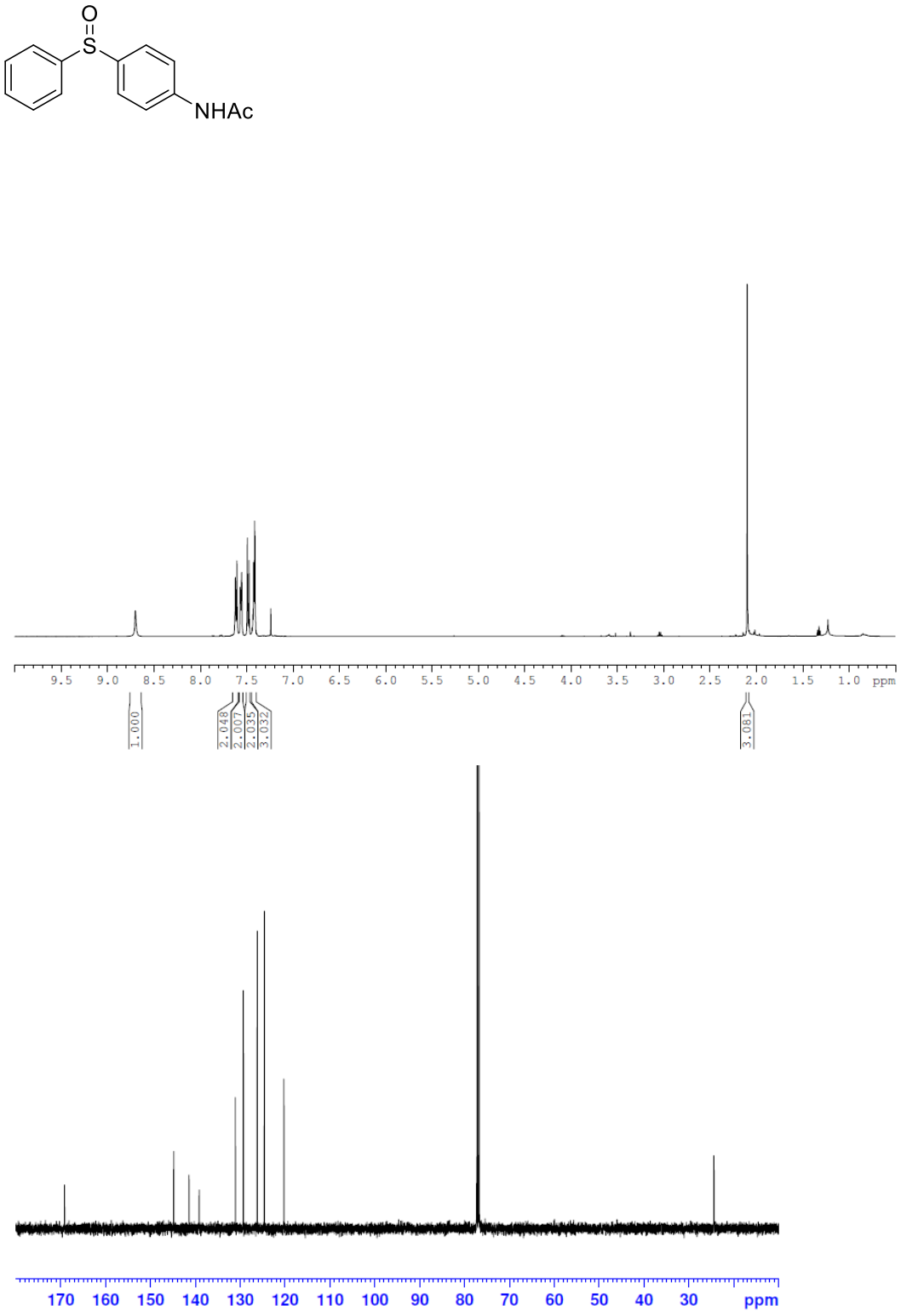


Figure A3.8. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3h** in $CDCl_3$.

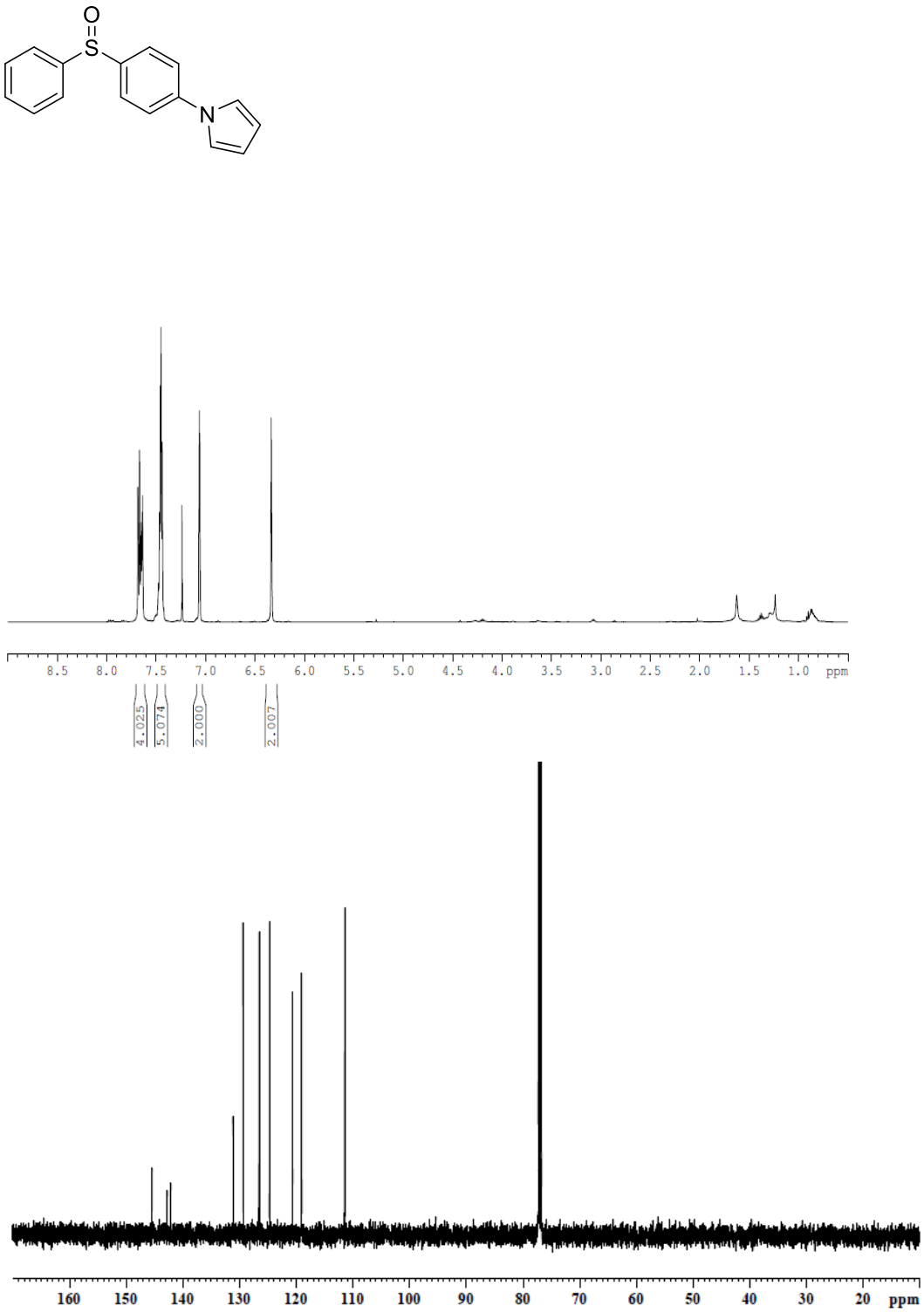


Figure A3.9. ^{1}H (500 MHz) and ^{13}C $\{^{1}H\}$ (125 MHz) NMR spectra of **3.3j** in $CDCl_3$.

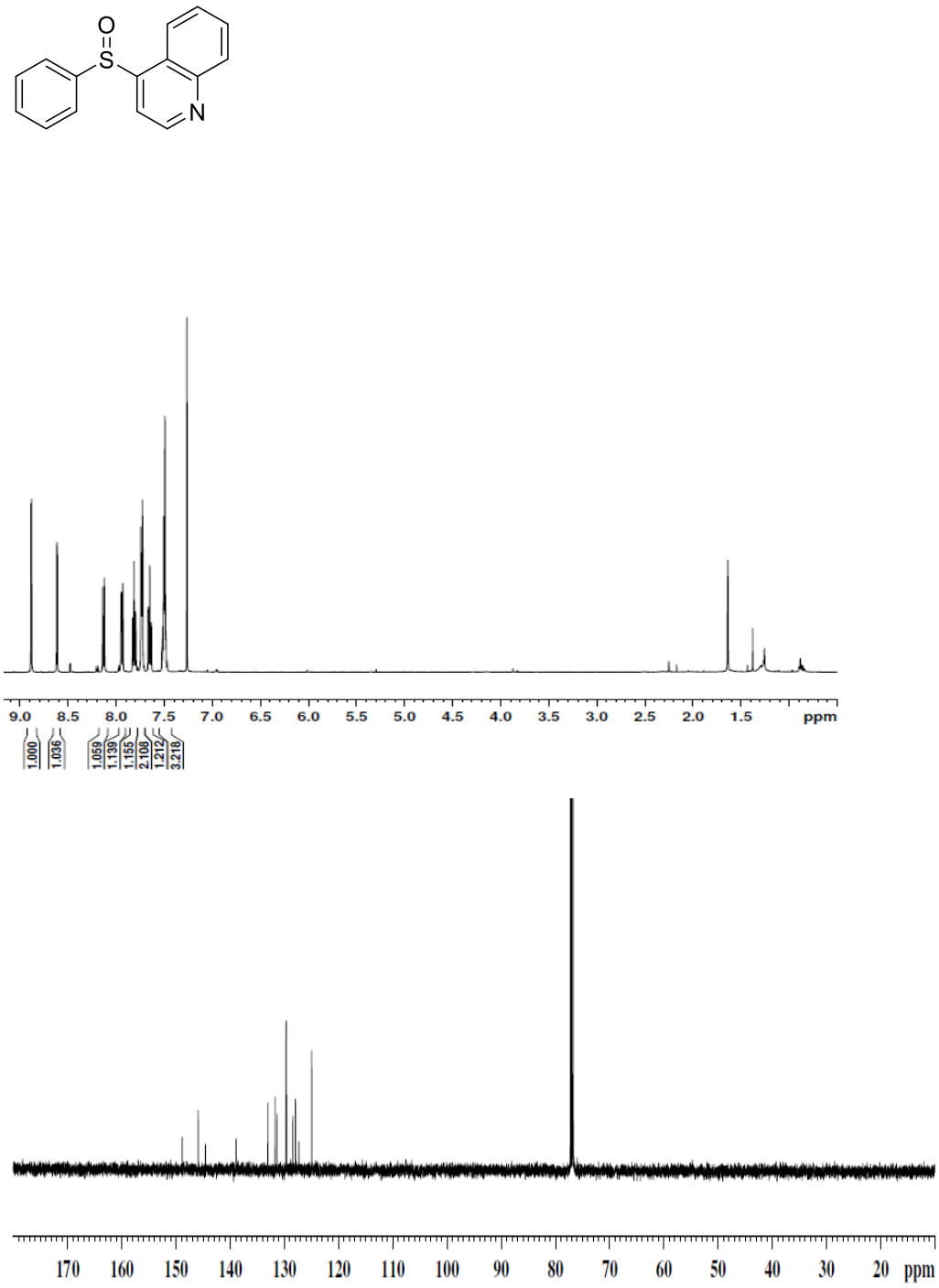


Figure A3.10. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3k** in $CDCl_3$.

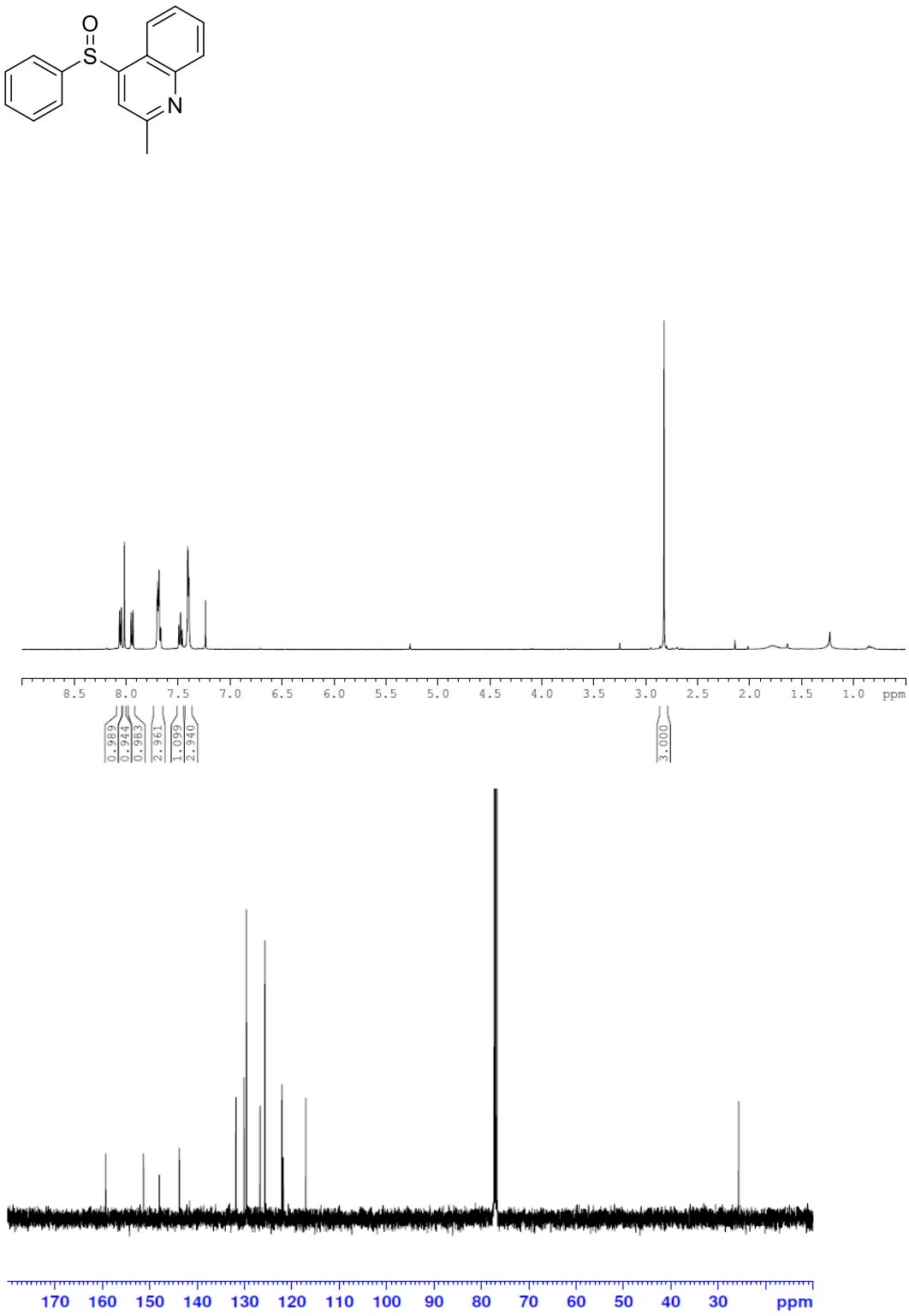
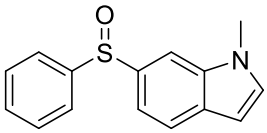


Figure A3.11. ^{1}H (500 MHz) and ^{13}C $\{^{1}H\}$ (125 MHz) NMR spectra of **3.3l** in $CDCl_3$.



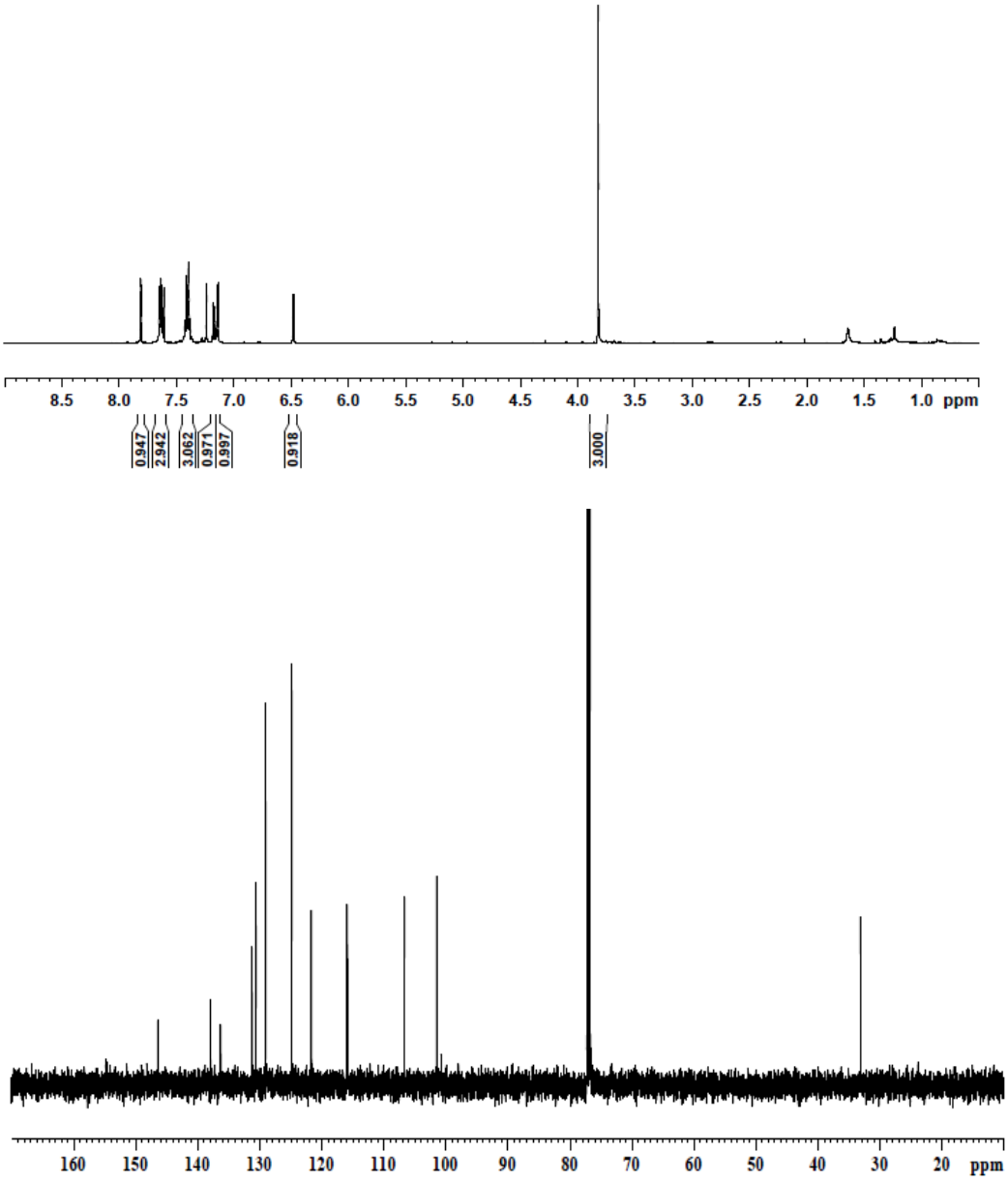


Figure A3.12. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3m** in $CDCl_3$.

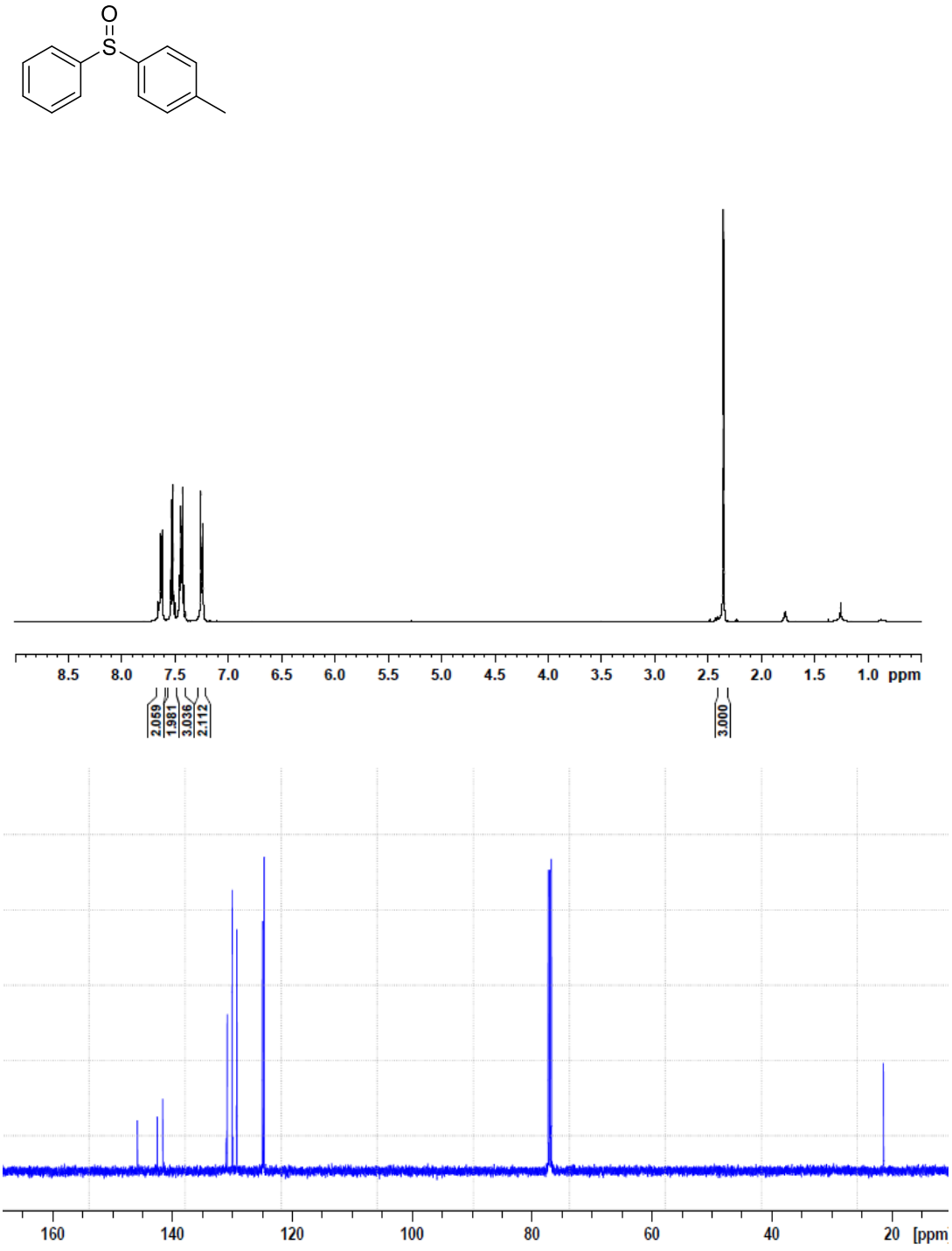


Figure A3.13. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3n** in $CDCl_3$.

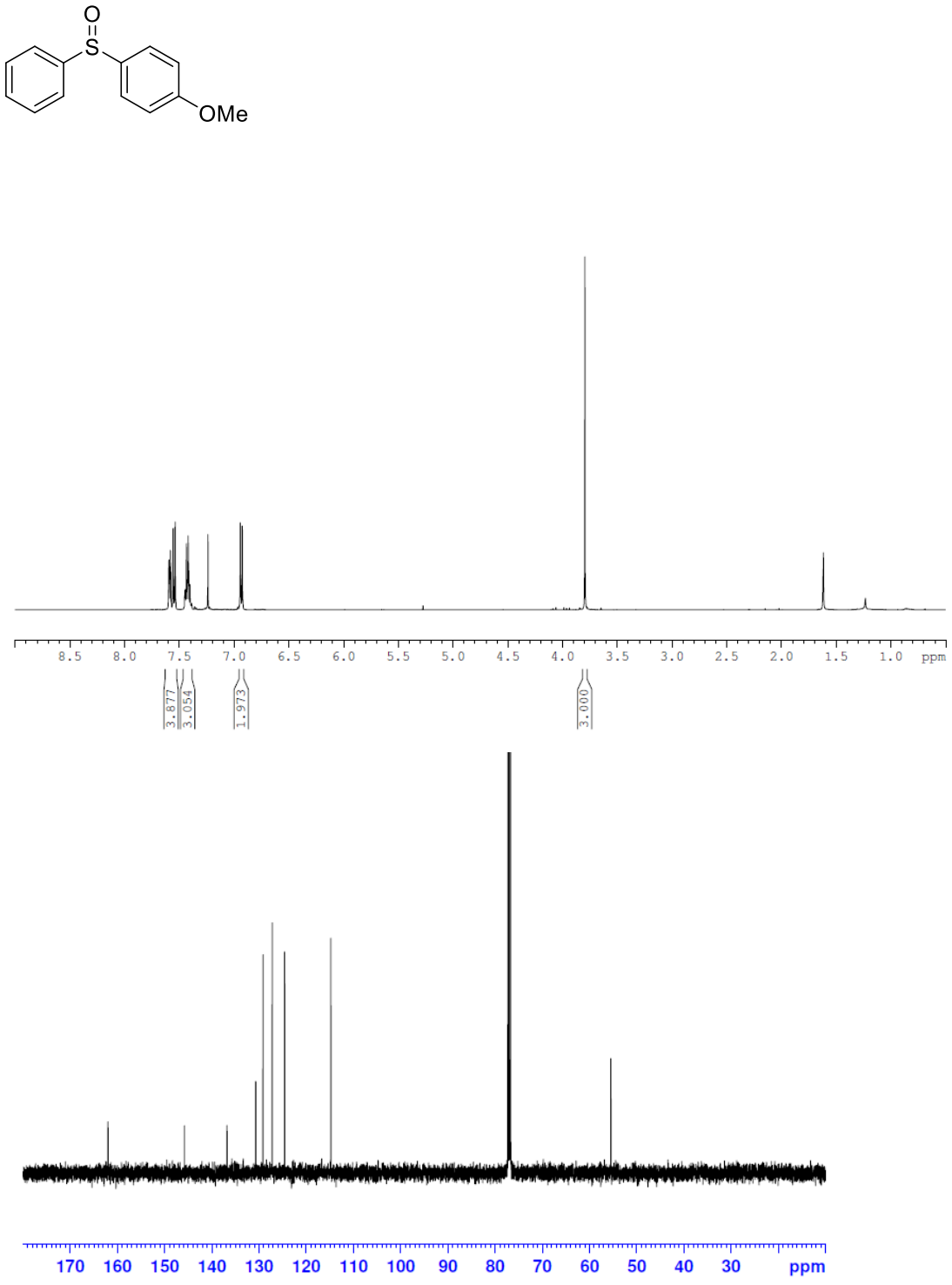


Figure A3.14. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3o** in $CDCl_3$.

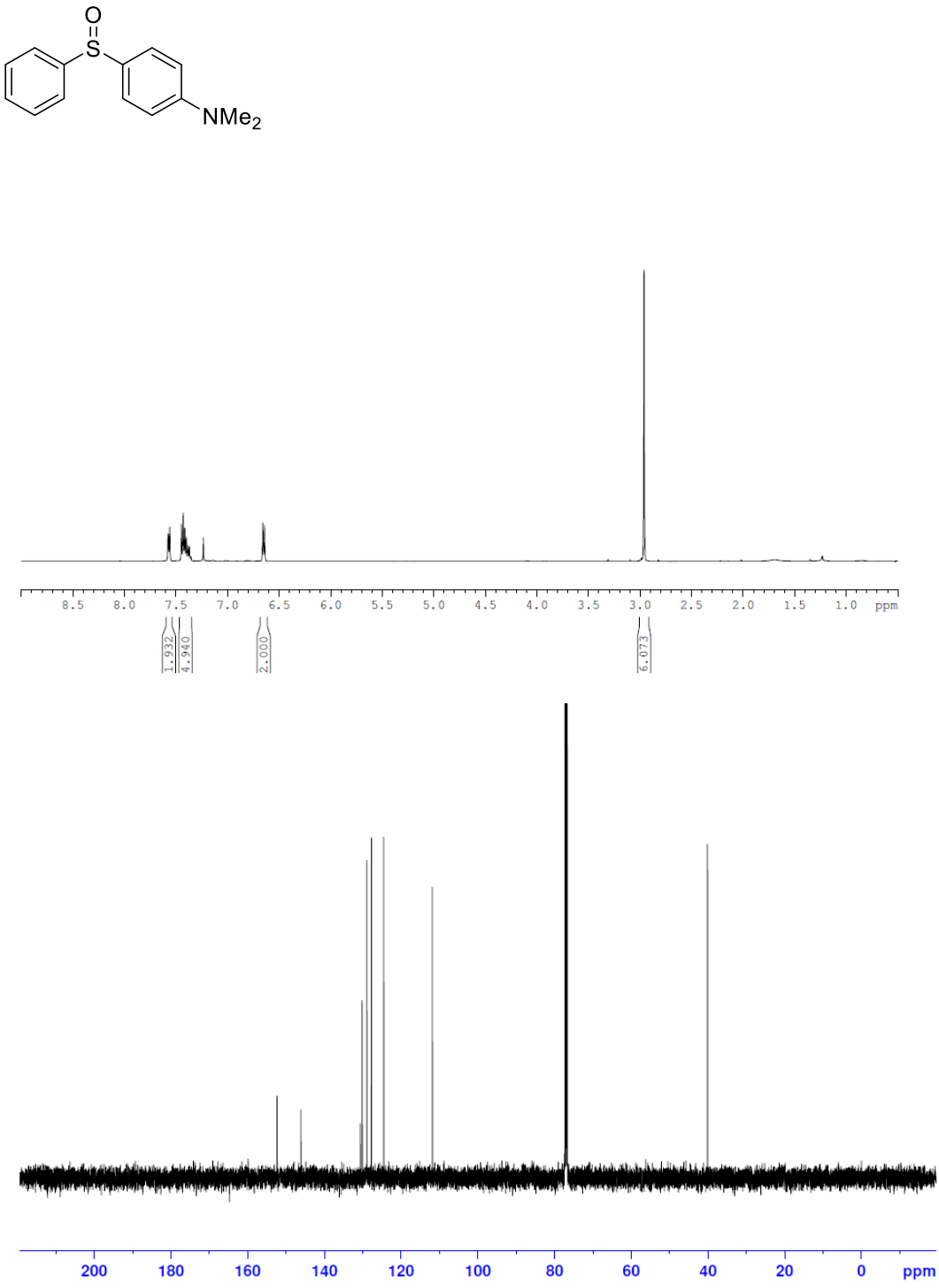


Figure A3.15. ^{1}H (500 MHz) and ^{13}C $\{^{1}H\}$ (125 MHz) NMR spectra of **3.3p** in $CDCl_3$.

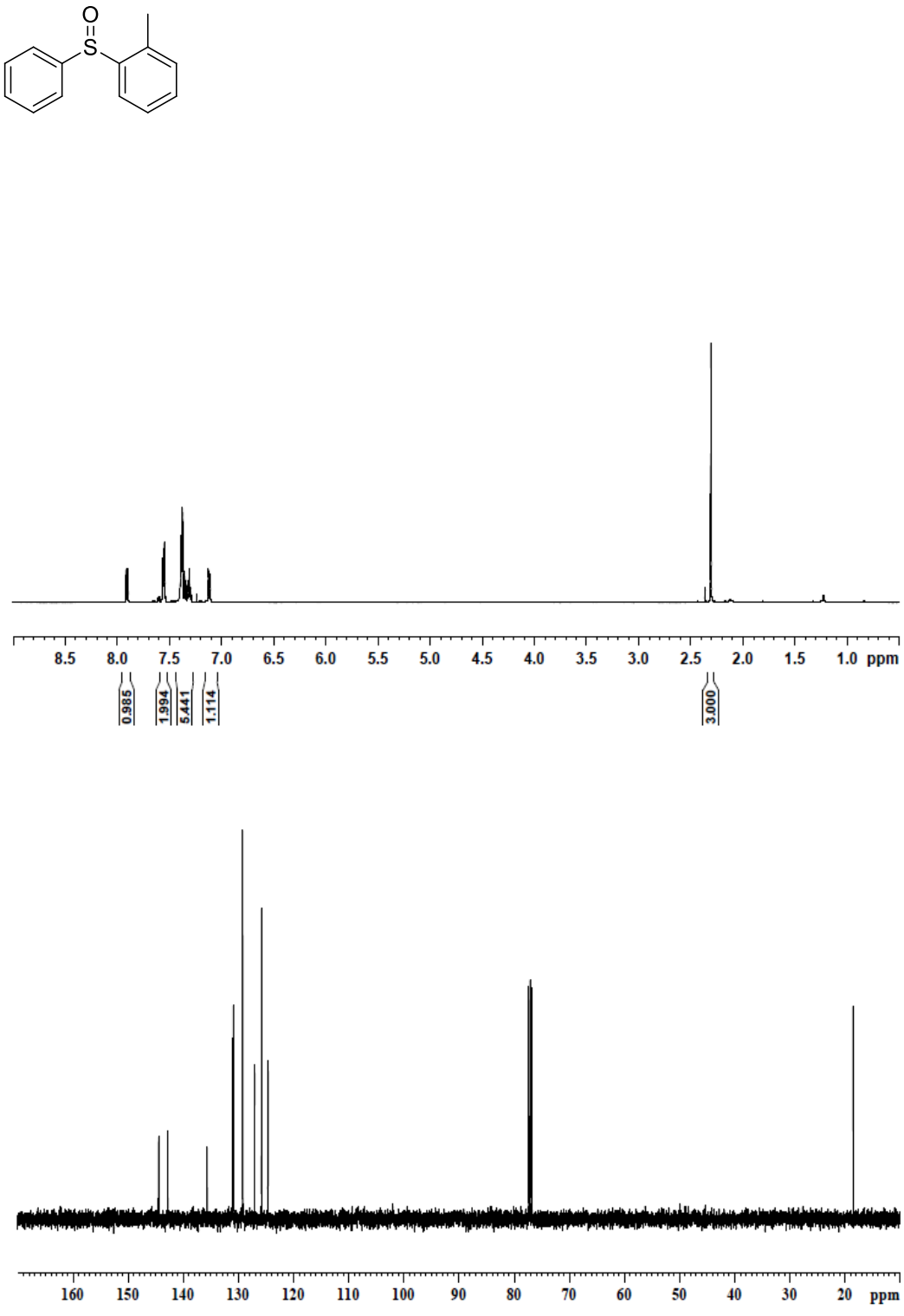


Figure A3.16. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3q** in $CDCl_3$.

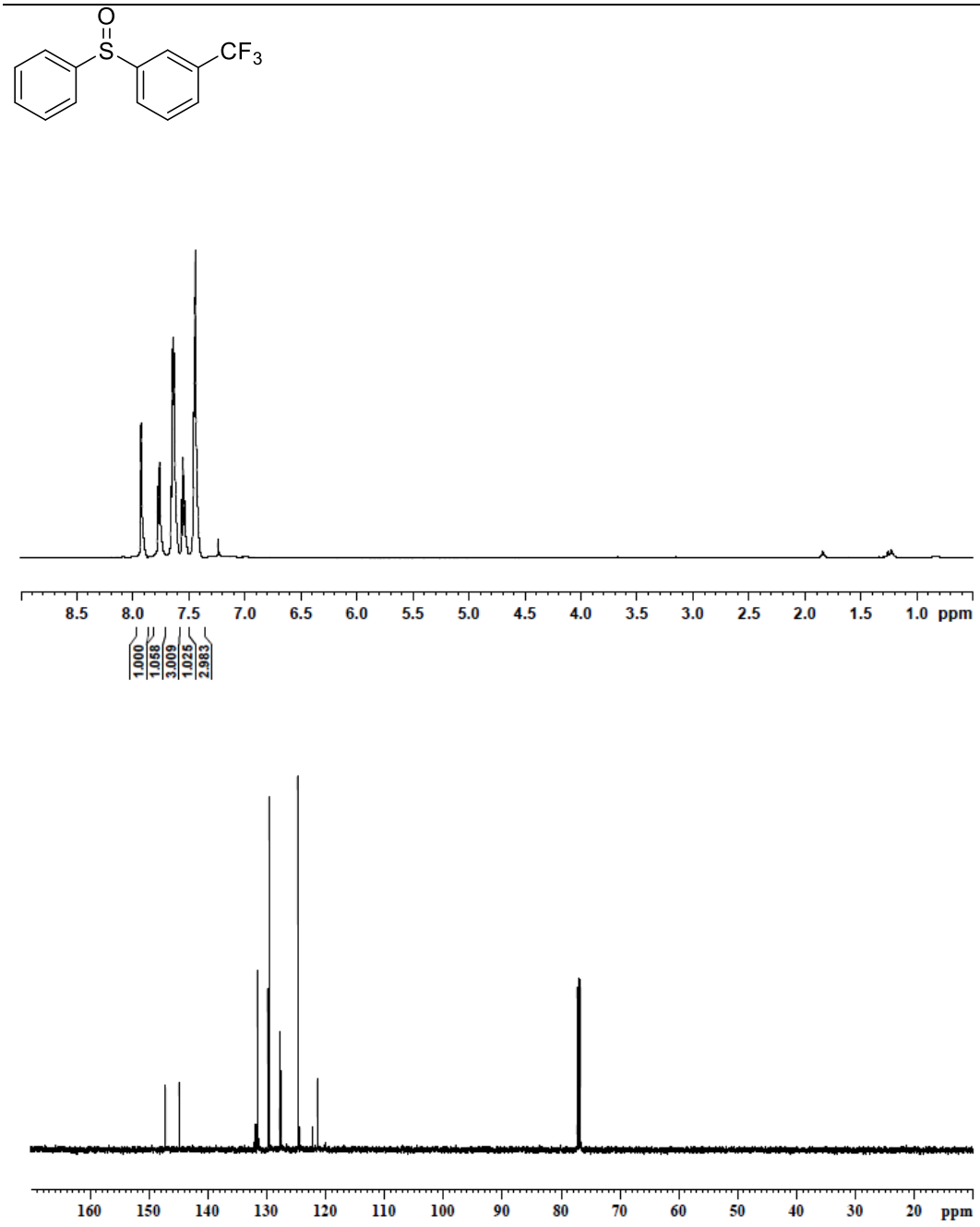


Figure A3.17. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3r** in $CDCl_3$.

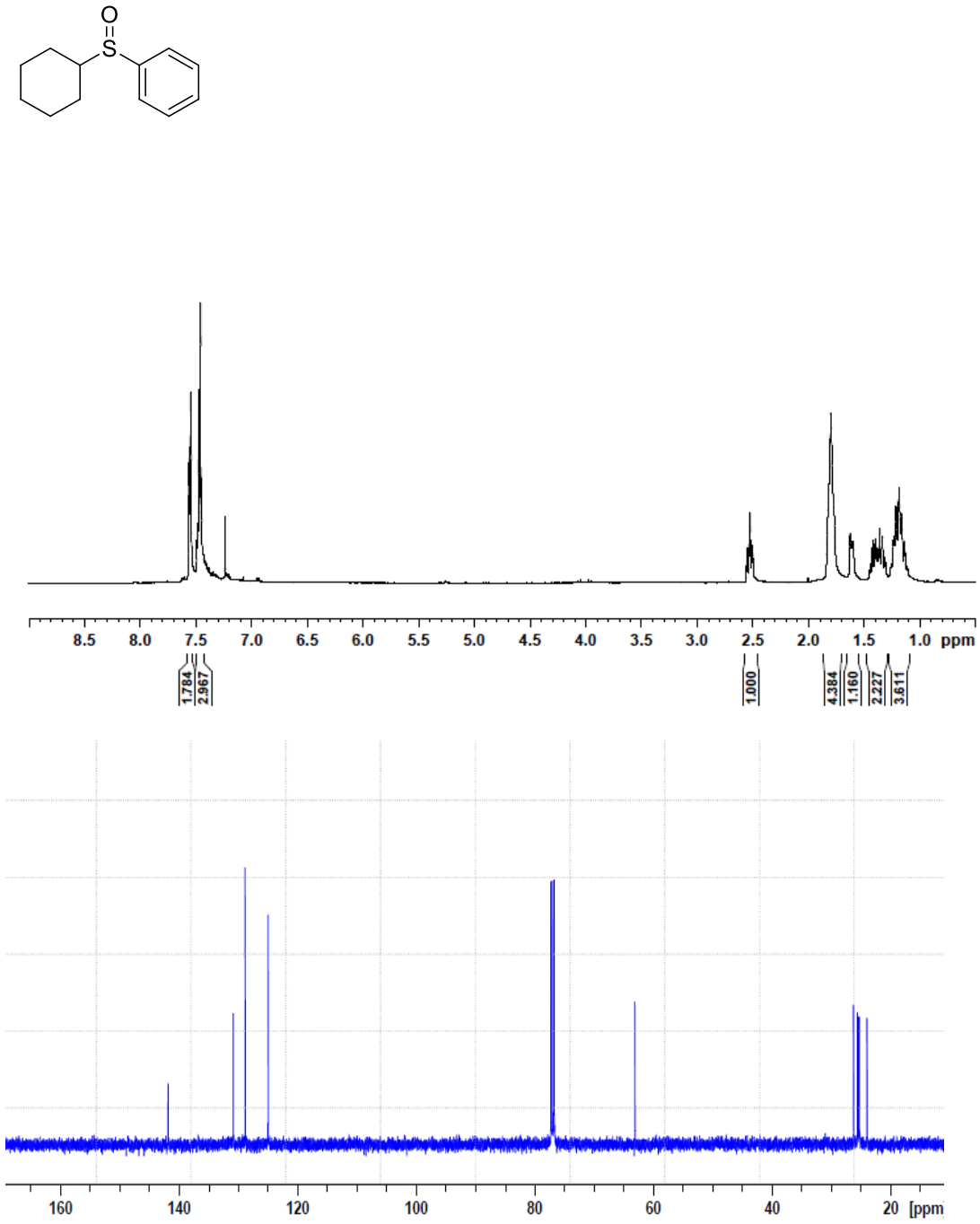


Figure A3.18. ^{1}H (500 MHz) and ^{13}C {^{1}H} (125 MHz) NMR spectra of **3.3r** in $CDCl_3$.